SYNTHESIS, ANTIMICROBIAL AND ANTIOXIDANT ACTIVITIES OF MANNICH BASES DERIVED FROM 1*H*-INDOLE-2,3-DIONE AND 3-AMINO-2-PHENYLQUINAZOL-4-ONE

Dissertation submitted to

The Tamil Nadu Dr. M.G.R. Medical University, Chennai

in partial fulfilment of the award of degree of

MASTER OF PHARMACY

(Pharmaceutical Chemistry)

Submitted by

JIJI JOSEPH OOMMEN

Under the guidance of

P. MANOJ KUMAR, M.Pharm.,
Department of Pharmaceutical Chemistry

MARCH - 2009

COLLEGE OF PHARMACY
SRI RAMAKRISHNA INSTITUTE OF PARAMEDICAL SCIENCES
COIMBATORE - 641 044.

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Place: Coimbatore
Date:

P. Manoj Kumar, M. Pharm.,
Department of Pharmaceutical Chemistry,
College of Pharmacy, SRIPMS,
Coimbatore – 44.

Certificate

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Place: Coimbatore
Date:

Prof. M. Francis Saleshier, M. Pharm.,
Head of the Department,
Department of Pharmaceutical Chemistry,
College of Pharmacy, SRIPMS,
Coimbatore – 44.

Certificate

This is to certify that the antimicrobial studies which was part of the dissertation entitled "SYNTHESIS, ANTIMICROBIAL AND ANTIOXIDANT ACTIVITIES OF MANNICH BASES DERIVED FROM 1*H*-INDOLE-2,3-DIONE AND 3-AMINO-2-PHENYLQUINAZOL-4-ONE" was carried out by JIJI JOSEPH OOMMEN in the Department of Pharmaceutical Chemistry, College of Pharmacy, Sri Ramakrishna Institute of Paramedical Sciences, Coimbatore which is affiliated to The Tamil Nadu Dr. M.G.R. Medical University, Chennai, under my supervision and co guidance to my fullest satisfaction.

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Date:

Prof. S. Krishnan, M. Pharm., Ph.D.,
Professor and Head,
Dept. of Pharmaceutical Biotechnology,
College of Pharmacy,
SRIPMS,Coimbatore-44.

Certificate

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Place: Coimbatore
Date:

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My dissertation entitled "SYNTHESIS, ANTIMICROBIAL AND ANTIOXIDANT ACTIVITIES OF MANNICH BASES DERIVED FROM 1*H*-INDOLE-2,3-DIONE AND 3-AMINO-2-PHENYLQUINAZOL-4-ONE" had become a successful one with the grace of the God and the prayers of my loved ones and the guidance of my guide.

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I express my sincere thanks to Library Staffs of SRIMPS, Coimbatore for providing library facilities during the course of my work.

I express my sincere gratitude to all my Classmates and friends especially Knolin, Mugeer, Manju, Bijosh, Mahalakshmi, Subhageetha, Arun Raj, Dhanya, Manikanda, Manjula, Shakila Banu and Juniors for their memorable company, support and timely help throughout my project work.

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I submit my sincere thanks to Mini Chechi and Niranjan Chetan M/s. Saraswathi Computer Center and M/s. Computer Park whose technical

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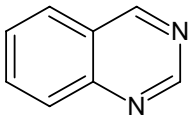
Above all I humbly place this work at the feet of the Almighty whose grace and mercy has helped me to complete this project successfully.

CONTENTS

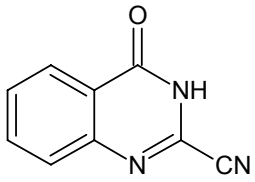
INTRODUCTION[1-8]

QUINAZOLINES

Quinazoline is a fused bicycle compound earlier known as benzo-1, 3-diazine. It was first prepared in the laboratory by Gabriel in 1903. One of its derivatives named 2-cyanoquinazolinone known much earlier was prepared from anthranilic acid and cyanogens.

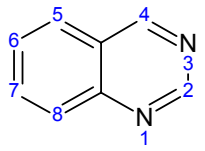


Quinazoline



2-cyanoquinazolinone

Paal and Bush suggested the numbering of quinazoline ring system, which is currently used.



The other less commonly used names for this ring system are phenmiazine and 5,6-benzopyrimidine. However, the name quinazoline is

now universally accepted.

The presence of a fused benzene ring alters the properties of the pyrimidine ring considerably. The two nitrogen atoms are not equivalent and the marked polarization of the 3, 4-double bond is reflected in the reactions of quinazolines.

The properties of the substituted quinazolines depends on:

a) Nature of the substituents

b) Whether they are in the pyrimidine ring or the benzene ring

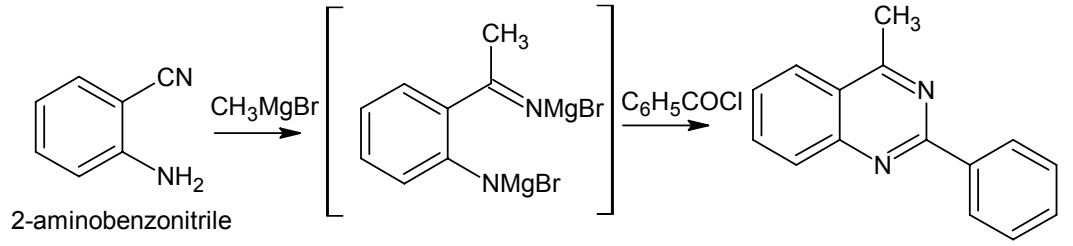
c) Whether or not complete conjugation is present in the pyrimidine ring.

METHODS TO PREPARE QUINAZOLINES:

I. From 2-aminobenzonitrile

1) With Grignard reagent:

2, 4-Disubstituted quinazolines are synthesized by the treatment of 2-aminobenzonitrile with Grignard's reagent where an intermediate is formed and this intermediate further reacts with acid chloride to give substituted quinazolinone.

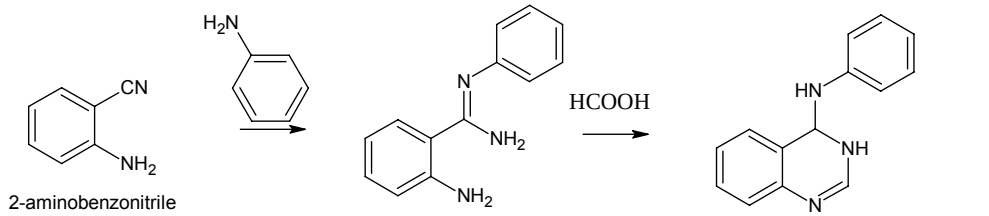


2-aminobenzonitrile

4-methyl-2-phenylquinazoline

2) With anilines in the presence of aluminium chloride:

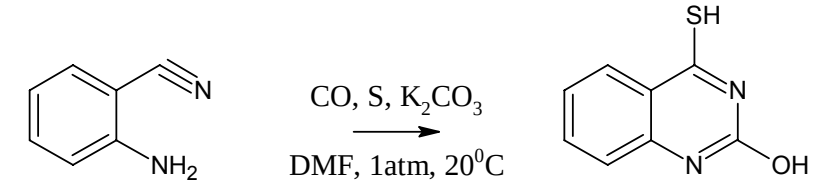
2-Aminobenzonitriles was treated with anilines in the presence of aluminium chloride to give an intermediate 2-amino-N-arylbenzamidines which when treated with formic acid gave 4-aryl aminoquinazolines.



2-aminobenzonitrile — 2-amino-*N*'-phenylbenzenecarboximidamide — *N*-phenyl-3,4-dihydroquinazolin-4-amine

3) In mild conditions:

Treatment of 2-aminobenzonitrile with carbon monoxide, sulphur and potassium carbonate in dimethylformamide at 1atm and 20^0C.

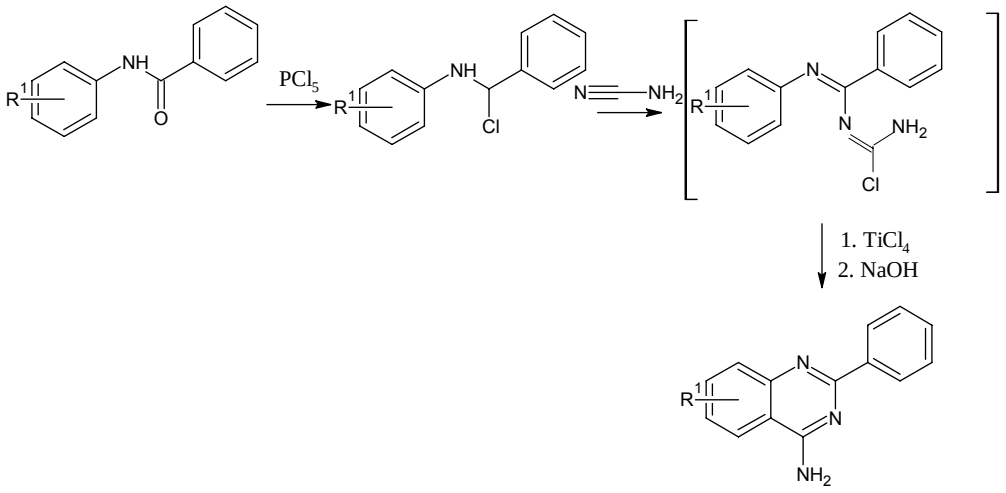


2-aminobenzonitrile — 4-sulfanylquinazolin-2-ol

II. From N- arylbenzamides:

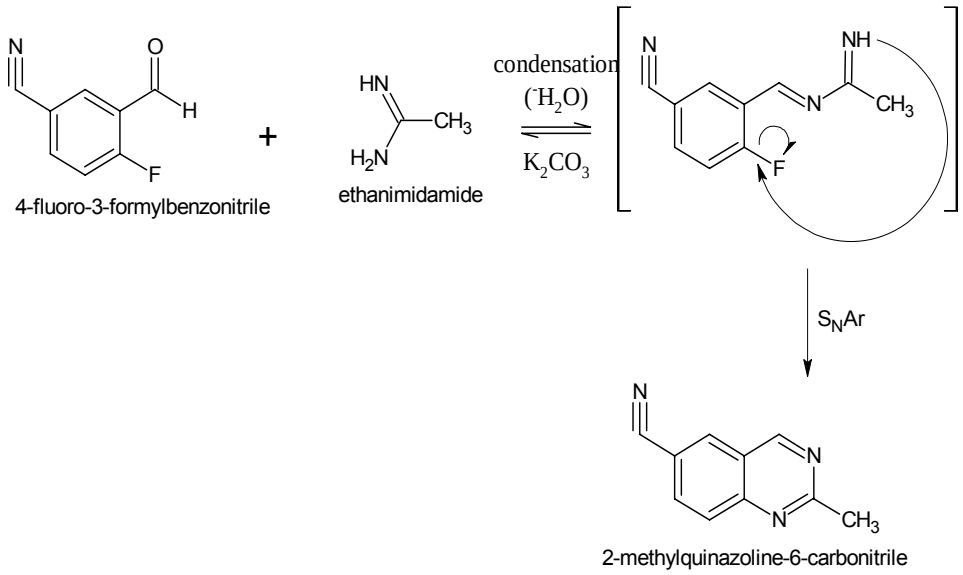
N-arylbenzamides when treated with phosphorus pentachloride yielded the corresponding N-arylbenzimidoyl chlorides which on treatment

with cyanamide yielded diaza-1, 3-butadiene as intermediates. Finally the diaza-1,3-butadiene upon the treatment with $TiCl_4$ underwent cyclisation to give the 2,4-disubstituted quinazolinones.



III. From 2- fluorobenzaldehydes:

2-Fluorobenzaldehydes which is activated by either a cyano or a nitro at the 5th position when treated with ethanimidamine forms 2-methylquinazoline 6-carbonitrile.

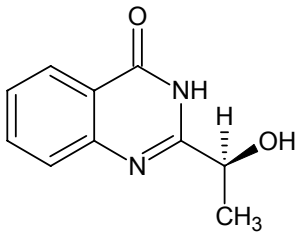


NATURAL SUBSTANCES CONTAINING THE QUINAZOLINE NUCLEUS:

Quinazoline alkaloids constitute a moderately sized group of natural products. These are some of the examples of alkaloids with the quinazoline moiety.

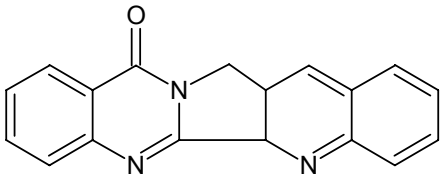
- Chrysogine:

This mould metabolite was isolated in 1973 by Hikino *et al.* from strains of *Penicillium chrysogenum.*



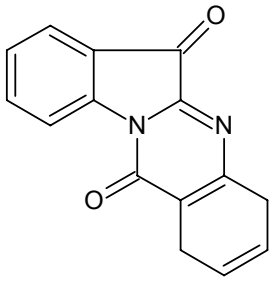
- Luotonin A:

This quinazoline alkaloid was isolated from the aerial parts of *Peganum nigellastrum,* a plant that has been used in traditional Chinese medicine as anti inflammatory.



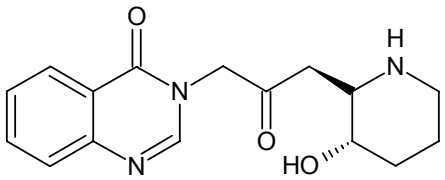
- Trypthanthrin:

This molecule was identified as a natural product from the plant kingdom in 1977 by Bergman *et al*. when it was isolated from the fruits of the cannon ball tree, *Couropita quianensis.*



- Febrifugine:

This alkaloid was isolated from the Chinese plant *Dichroafebrifuga*. These highly toxic molecules have attracted attention due to their potential anti malarial activity coupled with intricate structural problems of these relatively unstable compounds.

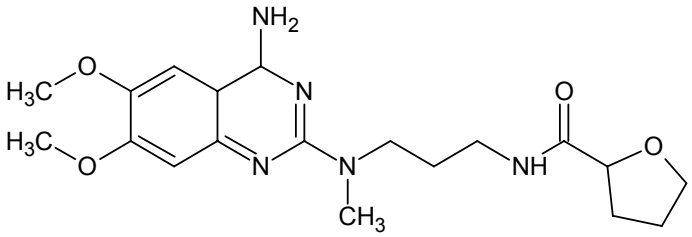


MEDICINAL QUINAZOLINE COMPOUNDS:

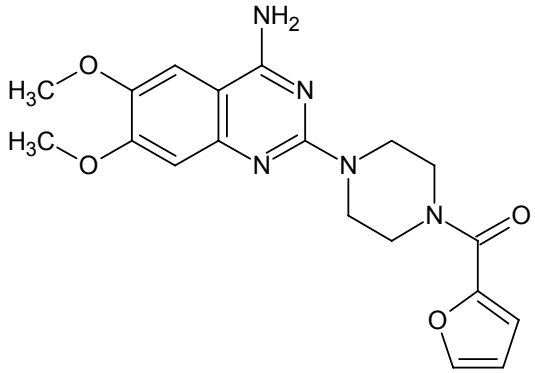
The quinazoline skeleton is present in a variety of biologically active compounds, among these are several marketed drugs.

- **Anti Hypertensive Drugs**

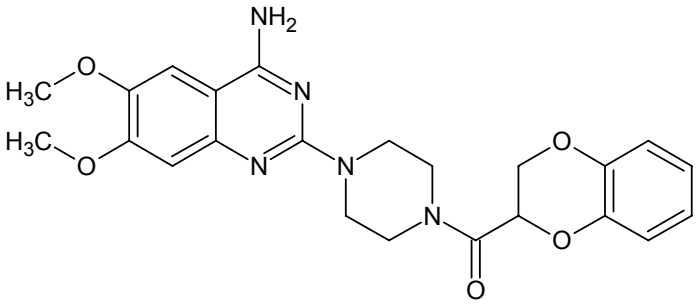
❋ ***Alfuzosine Hydrochloride:***



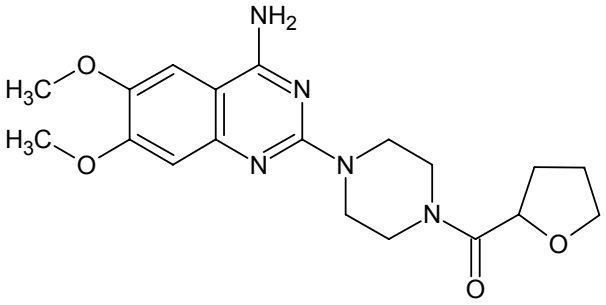
❋ ***Prazosine Hydrochloride:***



❋ ***Doxazosine mesylate:***

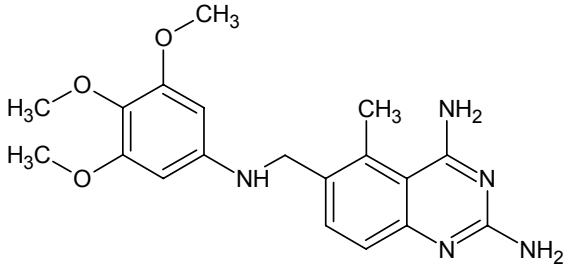


❋ **Terazosine hydrochloride:**



➢ **Dihydrofolate Reductase Inhibitor**

❋ ***Trimetrexate glucuronate:***

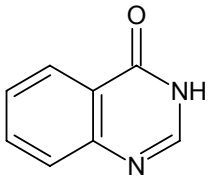


QUINAZOLINONES:

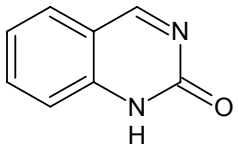
Of the many derivatives of quinazoline system known so far, keto-

quinazolines also called as quinazolinones, are the most important compounds. Depending upon the position of the keto or oxo group, these compounds may be classified into two types:

- 2(1H) quinazolinones (or) 1,2-dihydro-2-oxo quinazolines
- 4(3H)-quinazolines (or) 3,4-dihydro-oxoquinazolines.

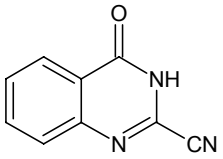


Quinazoline-4(3H)-one



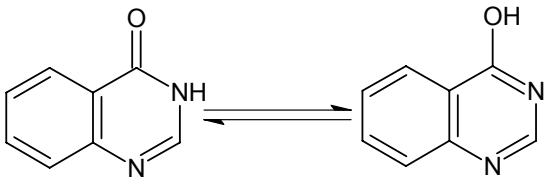
Quinazoline-2(1H)-one

2-Cyano-4(3H)-quinazolinone was the first quinazolinone derivative to be synthesized.



Brief account of reactivity of 4(3H)-Quinazolinones:

The amide linkage of quinazolinone show keto-enol tautomerism and the reaction characters of both keto and enol forms.



Keto form Enol form

Physical properties:

Quinazolinones are high melting crystalline solids, insoluble in

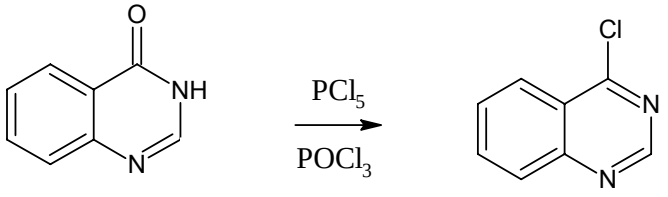
water and in most organic solvents but soluble in aqueous alkali. They are generally insoluble in dilute acids but are sometimes soluble in concentrated acids. 4(3H)-quinazolinones, although insoluble in dilute acids, are soluble in 6N hydrochloric acid. 4(3H)-quinazolinones form stable monohydrochlorides, chloroplatinate, chloroaurates and picrates and metal salts of silver, mercury, zinc, copper, sodium and potassium.

Stability of the ring system:

The ring system in quinazolinone is exceedingly stable in oxidation, reduction, hydrolysis reactions and other treatment designed to break the ring. There is no report of degradation of quinazolinone by simple chemical oxidation.

Aromatisation:

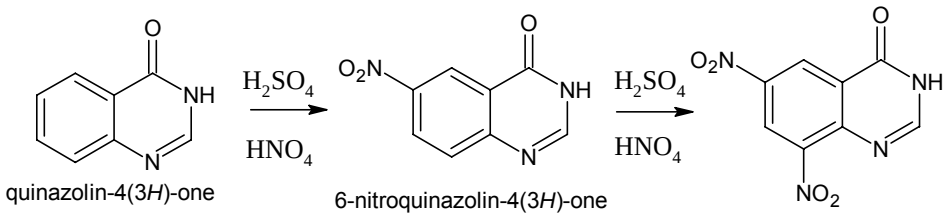
When 4-quinazolinone is heated with an equivalent amount of phosphorous pentachloride in phosphorous oxychloride, the corresponding 4-chloroquinazoline is obtained.



Nitration:

4(3H)-Quinazolinone on boiling with nitric acid undergoes

substitution to give 6-nitro-4-quinazolinone. On further nitration the second nitro group enters the 8-position to give 6, 8-dinitro derivatives.



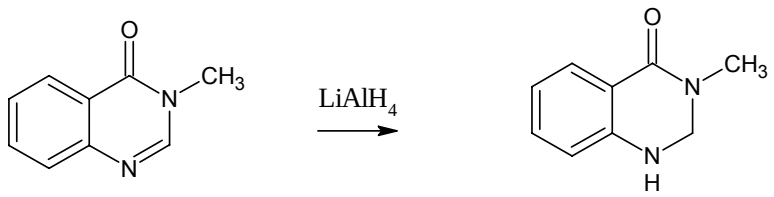
quinazolin-4(3*H*)-one

6-nitroquinazolin-4(3*H*)-one

6,8-dinitroquinazolin-4(3*H*)-one

Reduction:

2, 3-Dihydro-3-methyl- 4(1H)-quinazolinone could be obtained on reduction of 3-methyl-4(3H)-quinazolinone with Lithium Aluminium Hydride ($LiAlH_4$) in benzene.



3-methylquinazolin-4(3*H*)-one

3-methyl-2,3-dihydroquinazolin-4(1*H*)-one

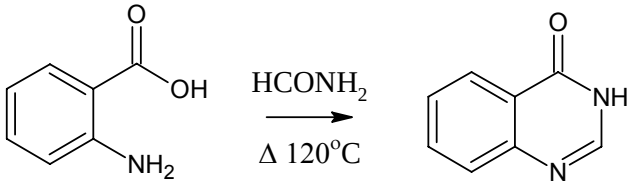
Methods of preparation of 4(3H)-Quinazolinones:

Most of the methods employed for the synthesis of 4(3H)-quinazolinones make use of anthranilic acid or one of their functional derivatives as the starting materials. Based on this factor, the general methods of synthesis are:

a. Condensation of anthranilic acid with acid amides:

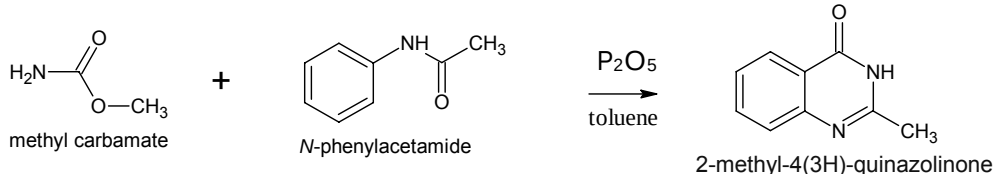
When anthranilic acid is heated in an open container with excess of formamide at 120°C, water is expelled and a nearly quantitative (90%)

conversion to 4(3H)-quinazolinones is achieved.



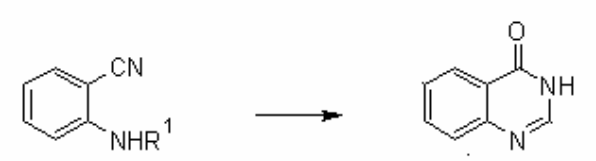
b. Condensation of acetanilides with urethanes:

Urethane and acetanilide on heating for 3 hours with phosphorus pentoxide in toluene gave 2-methyl-4(3H)-quinazolinone.



c. Oxidative hydration of o- aminobenzonitriles

o-Amino benzonitriles when treated with urea hydrogen peroxide(UHP) yields quinazoline-4(3H)-one.



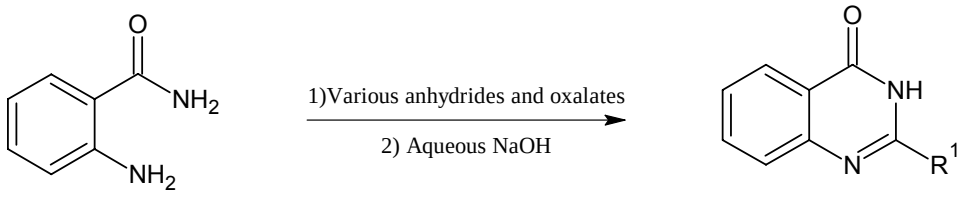
R^1=COR^4

Reagents and conditions: (a)-UPH, cat. K_2CO_3, acetone :water(1:1), reflux.

d. From anthranilamide:

Carboxylic acid derivative of quinazolinones is prepared from anthranilamide and benzoic anhydride, succinic anhydride, etc, which

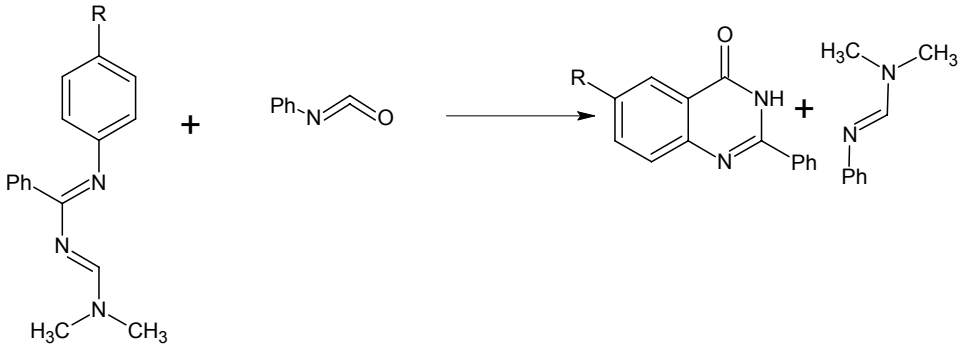
upon treatment with aqueous sodium hydroxide afforded the desired quinazolinones.



Where; R_1= phenyl, CO_2Et, $(CH_3)_2COOH$, $(CH_2)_3COOH$

e. Hetero-Diels-alder synthesis of 2-substituted-quinazolinones:

The synthesis of 2- substituted quinazolinones by the cyclisation of 1- aryl-4-dimethylamino-2-phenyl-1, 3-diaza-1, 3-butadienes and phenyl isocyanate was reported by Croce et al. The reaction was carried out under an atmosphere of nitrogen in toluene at reflux temperature, to furnish the desired products in good yields. The presence of the electron rich dimethyl amino group on the diene destabilizes the cycloaddition adduct, facilitating the elimination of the N, N-dimethyl-N'-phenylformamidine as a side product.

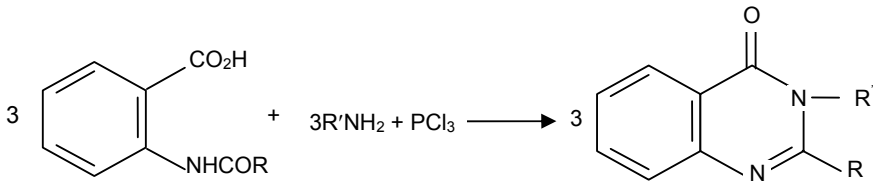


f. Niementowski Quinazoline Synthesis:

Formation of 4-oxo-3,4-dihydroquinazolines by cyclization of anthranilic acid and amides.

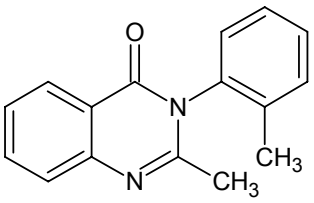
g. Grimmel,Guenther and Morgan's synthesis:

3 moles of *o*-amido benzoic acids,when heated with 3 moles of an amine together with one mole of phosphorous trichloride in toluene for two hours,gave high yields of 2,3-disubstituted 3,4-dihydro-4-oxoquinazolines.



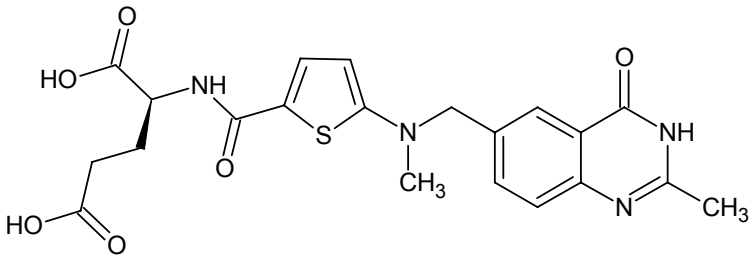
MEDICINAL DRUGS CONTAINING QUINAZOLINONE NUCLEUS:

❋ Methaqualone:



This compound was introduced in 1965 as a safe barbiturate substitute.

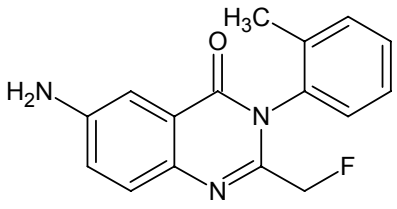
❋ Raltitrexed:



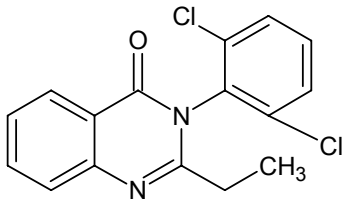
Thymidylate synthetase inhibitor (launched in 1996).

- **CENTRALLY ACTING MUSCLE RELAXANT**

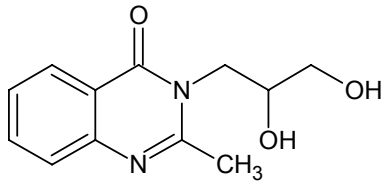
- Afloqualone:



- Chloroqualone:



- Diproqualone:



BIOLOGICAL IMPORTANCE OF 4-QUINAZOLINONES:

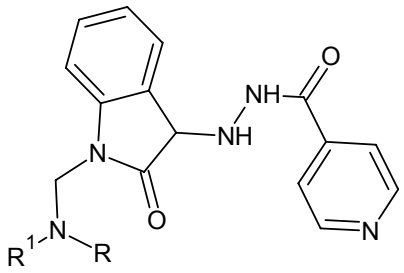
The quinazolinone skeleton is a frequently encountered hetrocycle in medicinal chemistry with activities including antibacterial[9-17], antifungal [18-22], analgesic and anti inflammatory[23-27], anticonvulsant[28,29], antihypertensive[30], antimalarial[31], anti HIV[32], cardiovascular [33], antiviral and anti cancer activity[34].

LITERATURE REVIEW

MANNICH BASE

1) Antimicrobial activity:

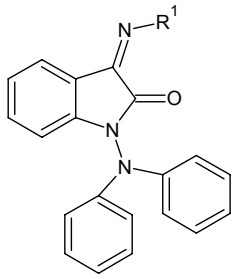
i) **P. S. Bhasin** *et al*.[35] synthesized a series of N-Mannich bases of isatin (indole-2,3-dione) and screened them for antibacterial and antifungal activity against 25 pathogenic bacteria and 5 pathogenic fungi. Most of the compounds showed moderate activity against all tested microbes.



ii) **R. P. Gupta** *et al*.[36] synthesized some mannich bases of isatin-3-(4'-phenyl-3'-thiosemicarbazone) and screened them for antibacterial activity against *E. Coli* and *Staphylococcus aureus.*

iii) **Sridhar S.K** *et al*.[37] synthesized a series of N-mannich bases from the Schiff's bases and hydrazones of substituted isatins and screened them for the antibacterial activity. Mannich bases

exhibited higher activity than corresponding schiff bases.

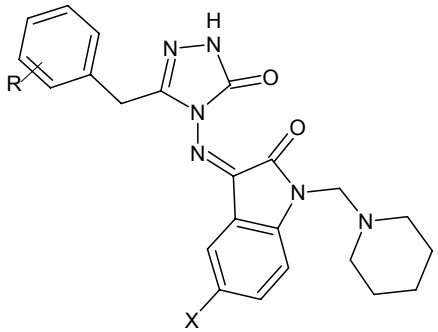


iv) **Pandeya S. N**. *et al*.[38] synthesized Schiff base of isatin with pyrimethamine and its N- Mannich bases and screened them against 25 pathogenic bacteria and 6 pathogenic fungi.

v) **S. A. Khan** *et al*.[39] synthesized a new series of N- mannich base of 3-semicarbazino isatin and these compounds showed remarkable antimicrobial activity.

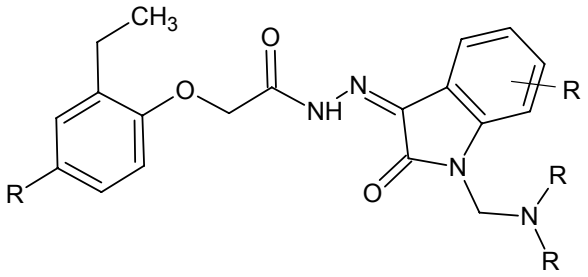
vi) **S. N. Pandeya** *et al*.[40] synthesized N- mannich bases of 3-[N^2–pyrimethaminylimino] isatin and reported them as potential antimicrobial agents.

vii) **Olcay Bekircan** *et al*.[41] synthesized Schiff and mannich bases of isatin with 4-amino-4,5-dihydro-1H-1,2,4 triazole-5-one and screened them for antimicrobial activity.

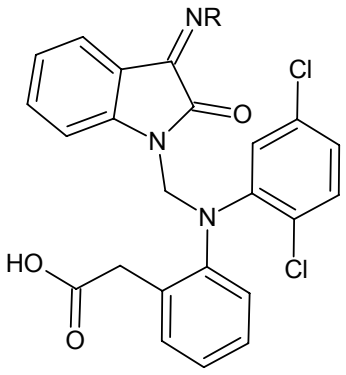


viii) **Mirjana Kupini** *et al*.[42] synthesized certain nitroisatin N-mannich bases and screened them for their antibacterial and antifungal activity.

ix) **R. P. Singh** *et al*.[43] synthesized certain mannich bases of isatin and screened them for their antimicrobial activity.



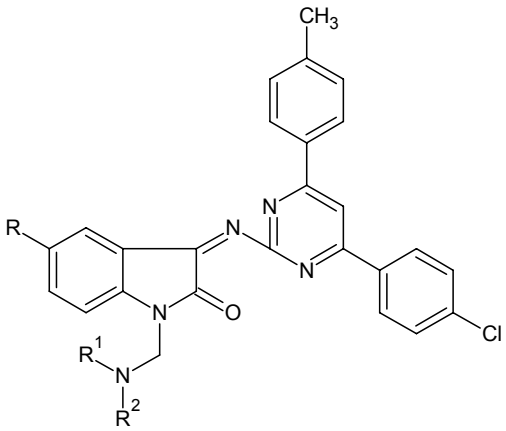
x) **V. Ravichandran** *et al*.[44] synthesized certain mannich bases of isatin and its derivatives with 2-[(2,6-dichlorophenyl) amino] phenyl acetic acid and screened them for antibacterial and antifungal activity. Most of the compounds showed moderate antibacterial activity and certain compounds showed good antifungal activity.



xi) **Surendra** *et al*.[45] sythesised certain N-Mannich bases of 3-[N'-

sulphadoximino]isatin and evaluated them for their antimicrobial activity.

xii) **S. N. Pandeya** *et al*.[46] synthesized certain mannich bases of isatinlyl pyrimidines and screened them for their antibacterial activity.

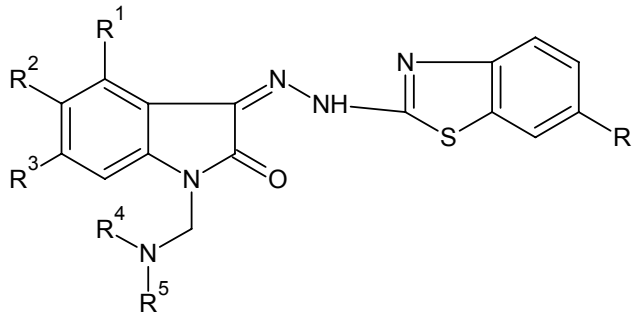


2) As anticonvulsants

i) **Sridhar S. K.** *et al*.[47] synthesized certain new mannich bases of isatin and were evaluated by maximal electroshock method (MES) and metrazol-induced convulsions (MET) at 30, 100 and 300 mg/kg dose levels. Eight compounds of the series exhibited significant anticonvulsant activity at 30 mg/kg dose level.

3) As antileishmanial agents

i) **R. S. Varma** *et al*.[48] synthesized certain mannich bases of isatin and were tested for antileishmanial activity. Some compounds showed 100% inhibition to *L. donovani*.



4) Mannich bases an analgesic, anti inflammatory and antipyretic

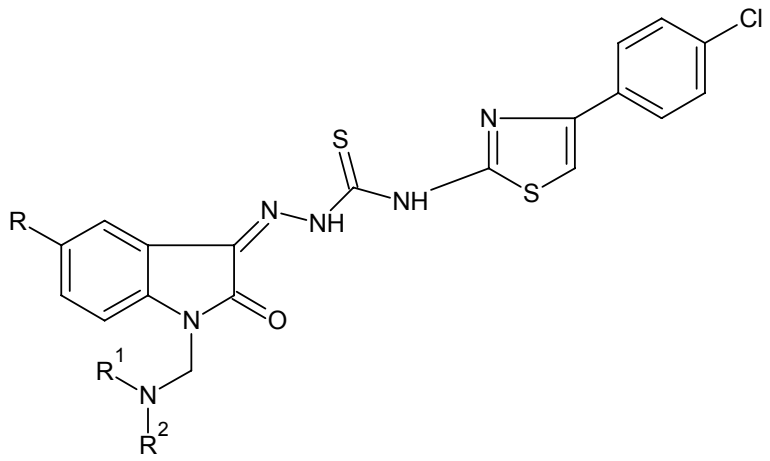
i) **S. K. Sridhar** *et al*.[49] synthesized N- mannich bases with the phenyl hydrazones of isatin. Out of the synthesized compounds about 5 compounds exhibited good activity.

5) As anti HIV agents

i) **S. N. Pandeya** *et al*.[50] synthesized certain mannich bases of isatin coupled with N-[6-chlorobenzothiazol-2-yl] thiosemicarbazide. These compounds were screened against HIV-1(IIIB) in MT4 cells.

ii) **S. N. Pandeya** *et al*.[51] synthesized N- mannich bases by treating 3-(4'-pyridyl)-4-amino-5-mercapto-4-(H)-1,2,4-triazole with Isatin (indole 2,3-dione) and its 5-chloro and 5-bromo derivatives to form Schiff bases and the N-Mannich bases and screened them for their anti HIV activity.

iii) **S. N. Pandeya** *et al*.[52] synthesized mannich bases from isatin derivatives and N-[4-(4'-chlorophenyl)thiazol-2-yl]thiosemicarbazide and were screened for their anti HIV activity.



6) As anticancer agents

i) Yogeeshwari P. *et al*.[53] synthesized mannich bases of isatin by treating them with formaldehyde and several isatin derivatives and these compounds were screened for their cytotoxic activity and some were found to be potent anticancer agent.

7) As antitubercular agents

i) S. N. Pandeya *et al*.[54] synthesized mannich bases of norfloxazin by treating them with formaldehyde and isatin and screened them against *Mycobacterium tuberculosis* most of the compounds showed promising activity.

PURPOSE OF WORK

Literature survey of quinazolinones showed these moieties to possess remarkable biological activities which includes antibacterial, analgesic, antifungal, CNS depressant activity etc.

Literature review shows that mannich bases of isatin exhibit broad range of activity. So it was planned to synthesize mannich bases having both quinazolinone and isatin moiety and check their biological activity.

Microwave mediated synthesis have gained considerable importance in the organic chemistry synthesis due to the short reaction time compared to the conventional heating method and increased

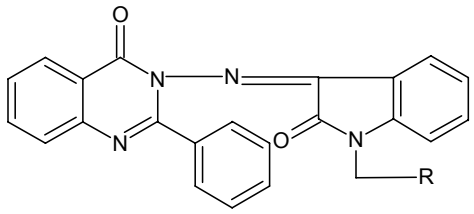
percentage yield of products. The present investigation consist of the following sections.

Part 1

Taking into consideration the above findings it was considered worthwhile to synthesize some new isatin based mannich bases of quinazolin-4-one.

General structure of mannich base undertaken in present study

a) 1- substituted methyl-3-(2-phenyl-4-oxo-3-quinazolinylimino)-1, 3- dihydro-indol-2-one.



Part 2

Spectral studies

Structure of newly synthesized compounds were to be confirmed from UV, IR, PMR and mass datas.

Part 3

Antimicrobial studies

The compounds synthesized were to be screened against selected gram (+)ve and gram (-)ve micro organisms and activities to be compared against a standard antibiotic. The prepared compounds were also planned to be subjected to antifungal screening and the activities compared with a standard antifungal agent.

Part 4

Antioxidant activity

The antioxidant activity of the synthesized compounds were to be evaluated and compared with the standard drug (ascorbic acid) by the DPPH method. The percentage antioxidant activity could be calculated by the formula given below:

Scavenging activity (AA %) = {[(Ab + As) – Am] / Ab} X 100%

Ab = Absorbance of 1.5 ml DPPH solution + 1.5 ml methanol

Am= Absorbance of 1.5 ml DPPH solution + 1.5 ml drug solution

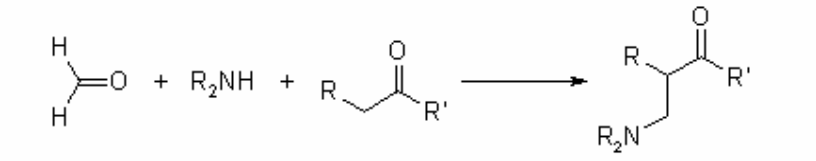
As= Absorbance of 1.5 ml drug solution + 1.5 ml methanol

CHEMISTRY

MANNICH BASE[55-58]

The mannich base is an amine, which is formed in the reaction of electrophilic imine salt and enol of carbonyl compound (usually ketone or aldehyde).The mannich reaction is an organic reaction which consists of an amino alkylation of an acidic proton placed next to a carbonyl functional group

with formaldehyde and ammonia or any primary or secondary amine. The final product is an β-amino carbonyl compound also known as the mannich base.



Mannich reaction enables two different molecules to be bonded together in one step. When an amino group is present in the substrate, intramolecular mannich reaction leading to cyclic compounds or to polymeric derivatives may occur. Hence this versatility of the mannich reaction, along with the remarkable possibilities of exploiting the reactivity of the mannich bases in producing further derivatives, makes it possible to attain the most varied chemical structures in conformity with the practical requirements and application needed in the industry.

The substrates suitable for the mannich reaction are available among a number of different compounds, and a very few limitations are found in the choice of the amine reactant, except the unreactive tertiary amine derivatives. The most significant chemical moieties that enable mannich reaction to be performed are listed below.

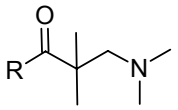
Substrates in the mannich reaction are in general, XH compounds having nucleophilic properties, with X being equal to C, N or other hetroatoms. CH compounds are suitably activated saturated and unsaturated derivatives and NH substrates may be amides, amines, hetrocycles, etc. Out of the OH substrates, alcohols are mainly able to give stable mannich products. Sulphur and phosphorus containing substrates are XH derivatives having the X atom bonded

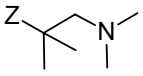
to the heteroatom in lower oxidation state like thiols, sulfinic acids and respectively, phosphine and phosphorus acid derivatives.

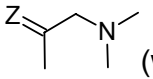
The mannich reaction is carried out on unusual substrates, characterized by molecules having very complex structures.

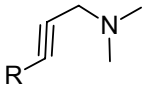
GENERAL CLASSIFICATION OF MANNICH DERIVATIVES ACCORDING TO SUBSTRATE AND AMINE TYPE.

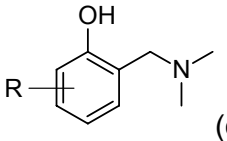
a) C – Mannich bases

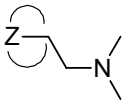
1. 

2.  (where Z= carboxy, N-hetroaryl, Nitro group, etc)

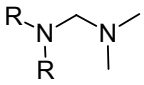
3.  (where Z=R_2C, R-N)

4. 

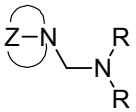
5.  (or NH- activated benzene ring)

6.  (Z= N, O, etc.) hetrocycle

b) N- Mannich bases

1. 

2.  (Z= O, S)

3.  (hetrocycle)

c) O-, S- etc. Mannich bases

1. R-O-CH_2-N<
2. R-S-CH_2-N<
3. R-SO_2-CH_2-N<

COMPONENTS OF A MANNICH REACTION:

The three important reactants in a mannich reaction are:

a) compounds containing reactive hydrogen atom

b) amines

c) aldehydes

A. THE COMPOUNDS CONTAINING REACTIVE HYDROGEN ATOM:

i) Ketones:

This includes all ketones possessing –CO.CH< group. Unsymmetrical ketones react predominantly at the higher substituted alpha position.

ii) Acids and their esters:

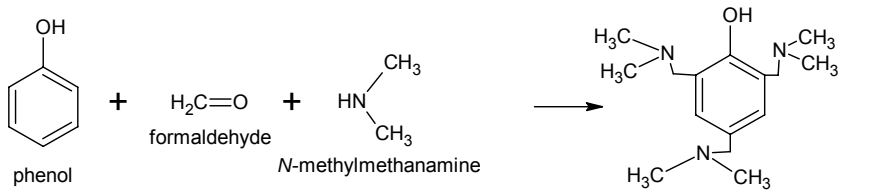
A number of acids containing highly active hydrogen atom in the alpha position can be used instead of aldehydes and ketones. When an acid is employed, the free secondary amine, rather than the salt, is used.

Example : 1) with ethyl malonic acid

$C_2H_5CH(COOH)_2 + CH_2O + (CH_3)_2NH \rightarrow C_2H_5C(COOH)_2.CH_2N(CH_3)_2$

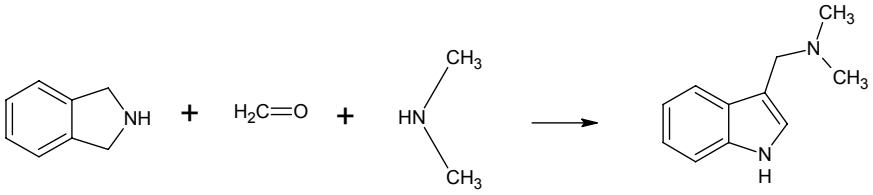
iii) Phenols:

The *o*- and *p*- hydrogens in phenols are sufficiently acidic to enter the mannich reaction.

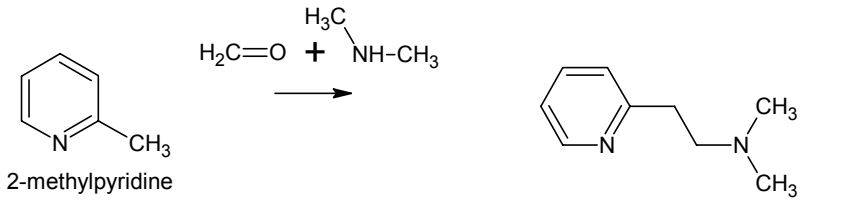


2,4,6-tris[(dimethylamino)methyl]phenol

iv) Furan, pyran, indole and their derivatives: These compounds are sensitive to acids and hence the reaction must be carried out in the presence of a weak acid like acetic acid.



v) Methylated pyridines and quinazolines

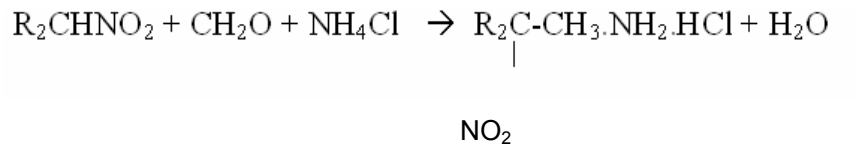


2-methylpyridine

N,*N*-dimethyl-2-pyridin-2-ylethanamine

vi) Nitro compounds:

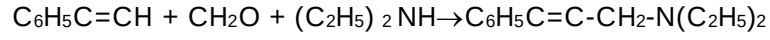
Primary and secondary nitro compounds undergo the mannich reaction.



$$R_2CHNO_2 + CH_2O + NH_4Cl \rightarrow R_2C(NO_2)\text{-}CH_3.NH_2.HCl + H_2O$$

vii) Acetylenes

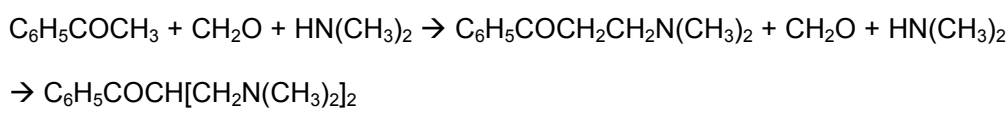
Phenyl acetylene and some of its nuclear substituted derivatives react readily with formaldehyde and secondary amines.



$$C_6H_5C{\equiv}CH + CH_2O + (C_2H_5)_2NH \rightarrow C_6H_5C{\equiv}C\text{-}CH_2\text{-}N(C_2H_5)_2$$

In certain cases like acetophenone if the compound contains a second reactive hydrogen, further reaction may occur with the introduction of another $-CH_2\text{-}NR_2$ group.

Example:



$C_6H_5COCH_3 + CH_2O + HN(CH_3)_2 \rightarrow C_6H_5COCH_2CH_2N(CH_3)_2 + CH_2O + HN(CH_3)_2 \rightarrow C_6H_5COCH[CH_2N(CH_3)_2]_2$

B) AMINES:

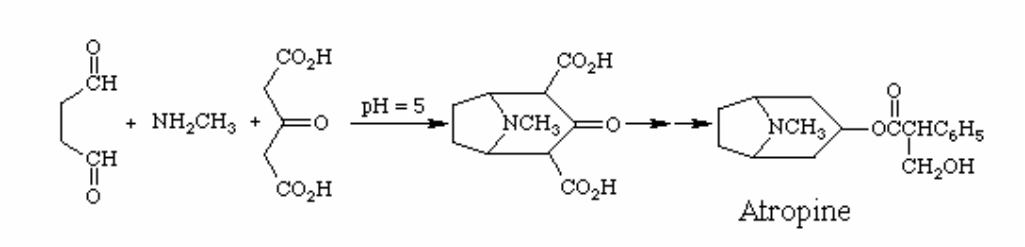
The amine may be primary or secondary but the most convenient are secondary amines since they possess only one replaceable hydrogen. If a

primary amine is used, a secondary amine is formed which further react to give tertiary amines.

$CH_3COCH_3 + CH_2O + NH_2CH_3 \rightarrow CH_3COCH_2CH_2NHCH_3 + CH_2O + CH_3COCH_3 \rightarrow CH_3N(CH_2CH_2COCH_3)_2$

C) ALDEHYDES:

Formaldehyde is the most frequently used aldehyde. Higher aldehydes like succinaldehyde are also used in the Robinson synthesis.



FURTHER REACTIONS OF MANNICH BASE:

The mannich base obtained can further react in many ways

a. If a primary or secondary amine is used, the mannich base may condense with one or two additional molecules of aldehyde and acdtive compound.

$$H_2NCH_2CH_2COR \xrightarrow[CH_3COR]{HCHO} HN(CH_2CH_2COR)_2 \xrightarrow[CH_3COR]{HCHO} N(CH_2CH_2COR)_3$$

b. If the active hydrogen compound has two or three active hydrogens, the mannich base may condense with one or two additional molecules of aldehyde and ammonia or amine.

E.g.

$H_2NCH_2CH_2COR \rightarrow (H_2NCH_2)_2HCOR \rightarrow (H_2NCH_2)_3COR$

c. Sometimes mannich base may react with excess of formaldehyde.

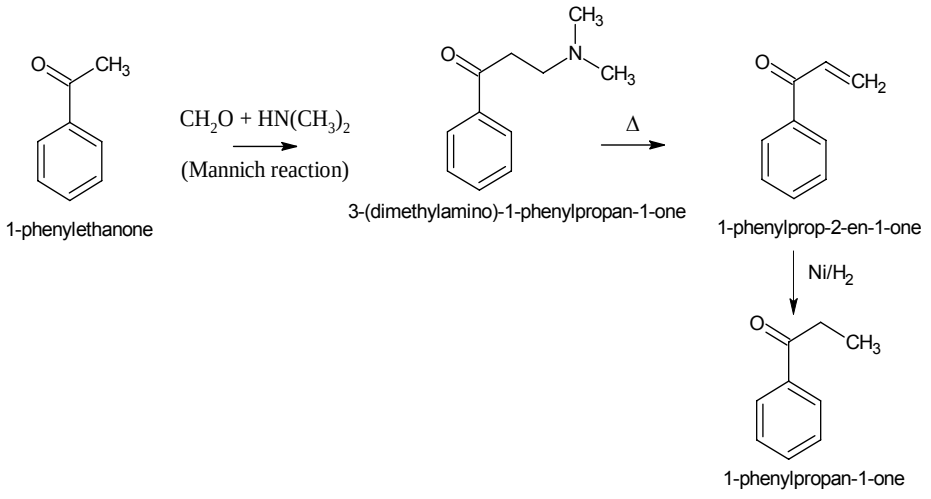
$H_2NCH_2CH_2COR + HCHO \longrightarrow H_2C{=}NCH_2CH_2COR$

APPLICATIONS OF MANNICH BASES:

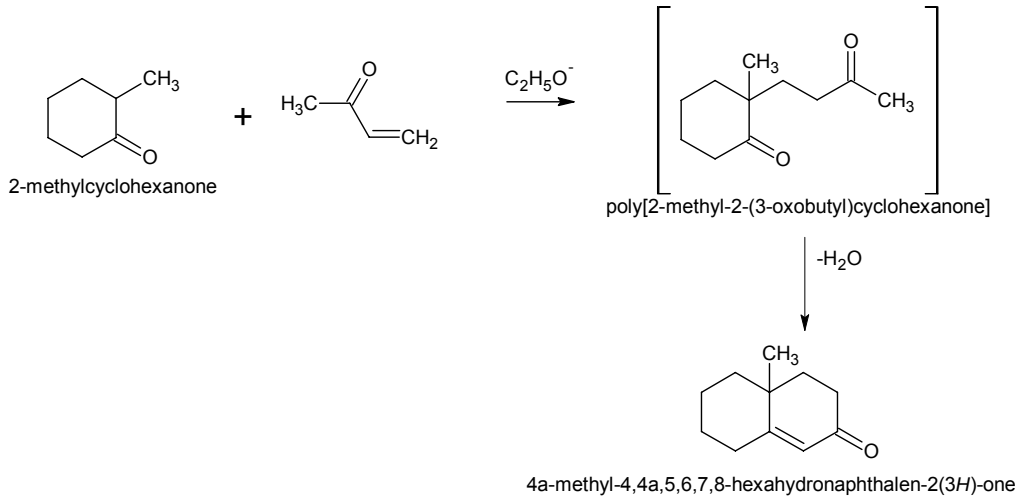
a) Mannich base as an intermediate in synthesis:

i) In the conversion of ketone to its next higher homologue:

Reduction of the unsaturated ketone obtained by the decomposition of a mannich base leads to a ketone with one more methylene group than that used in the preparation of the mannich base.

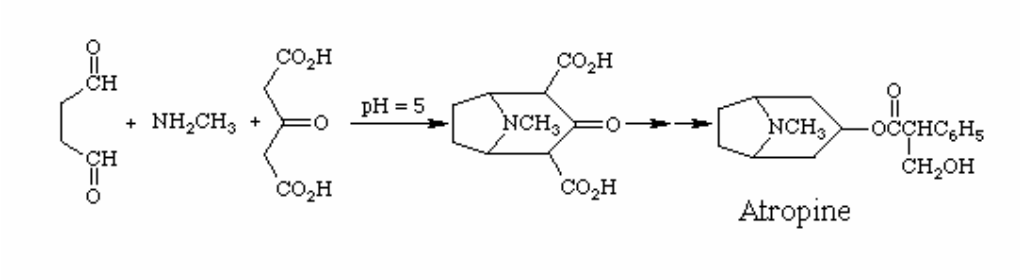


ii) In building the ring systems for steroids(Robinson's ring extension):



b) Synthesis of natural products:

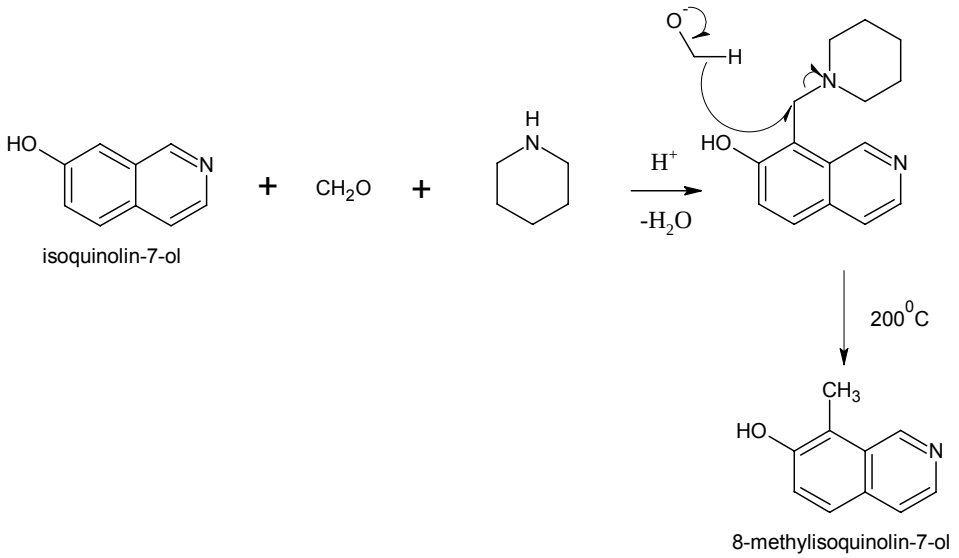
i) Synthesis of atropine(Robinson's synthesis):



ii) Synthesis of quinine:

In the synthesis of quinine the introduction of the methyl group into the 8th position of the 7- hydroxyisoquinoline was done through mannich reaction.

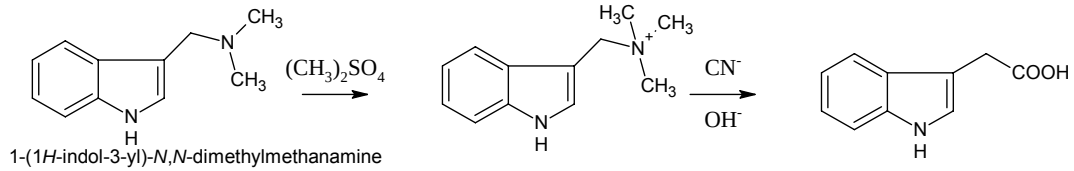
Reduction of the 8-methyl derivative was brought about by sodium methoxide at high temperature (hydride-ion transfer).



iii) From Gramine (Mannich base of indole):

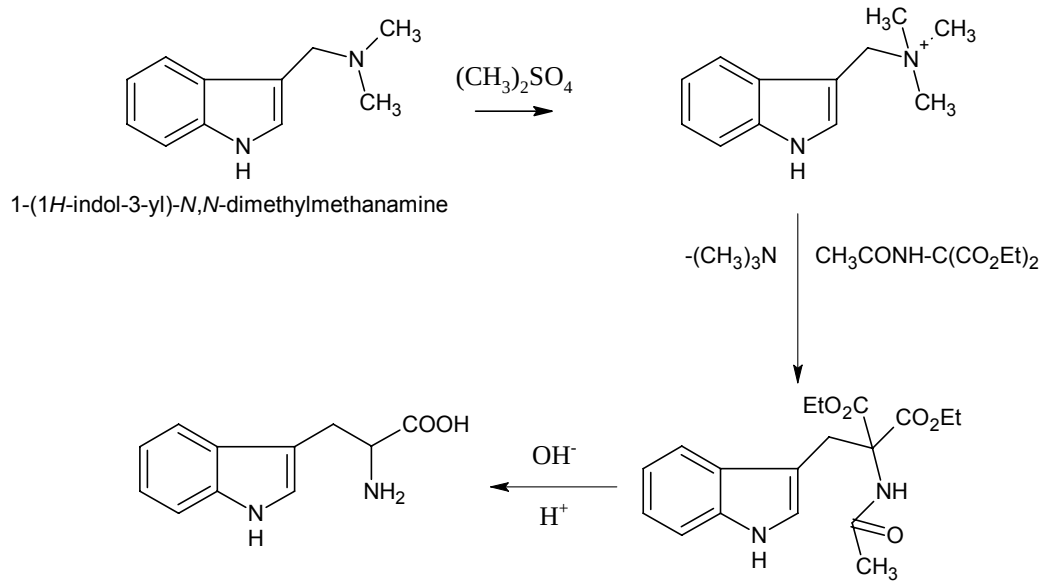
a) Synthesis of heteroauxin:

Gramine on methylation with dimethylsulphate followed by the treatment with cyanide ion and then hydrolysis gives Heteroauxin.



1-(1*H*-indol-3-yl)-*N*,*N*-dimethylmethanamine

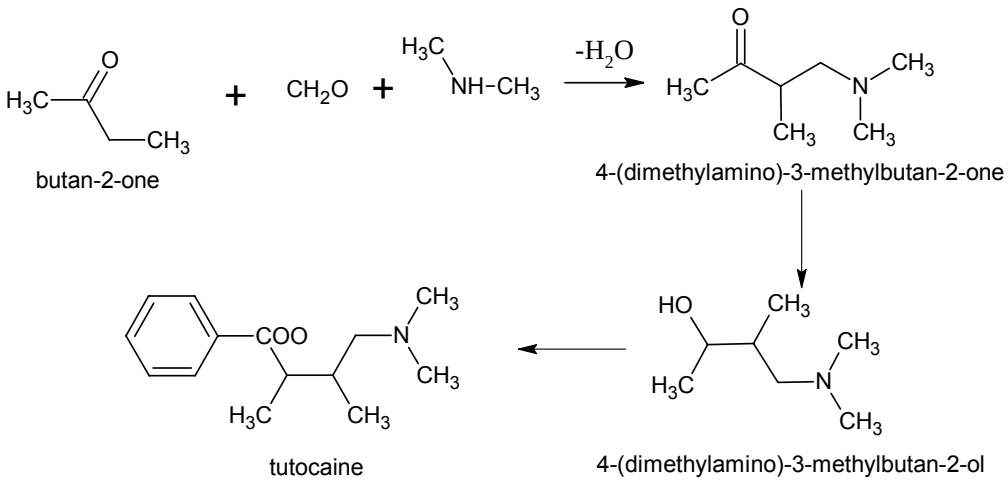
b) Synthesis of tryptophan:



1-(1*H*-indol-3-yl)-*N*,*N*-dimethylmethanamine

c) Synthesis of medicinal compounds:

i) Local anaesthetic (tutocaine):



MECHANISMS INVOLVED IN THE FORMATION OF MANNICH BASE:

Mannich reaction:

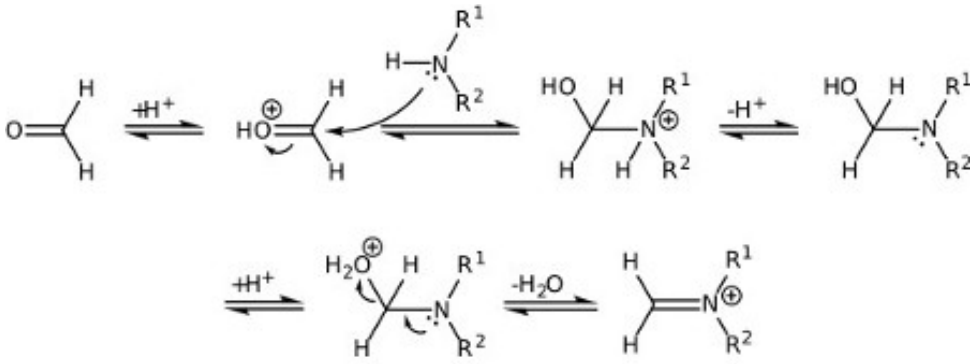
It is a reaction in which compounds having active hydrogen react with non-enolizable aldehydes and ammonia or primary or secondary amines to give aminomethylated products /mannich bases**.**

MECHANISM INVOLVED:

Acid catalyzed reaction:

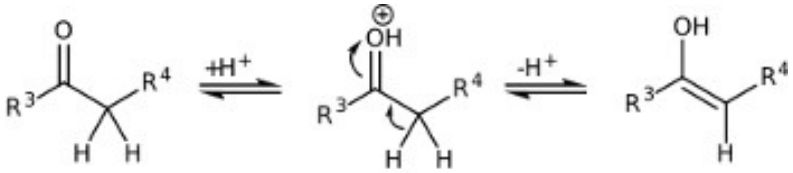
STEP I

The lone pair of electrons on the nitrogen atom of the amine attacks the carbonyl group of the formaldehyde in the presence of acid to give an adduct, which eliminate water to form electrophile.



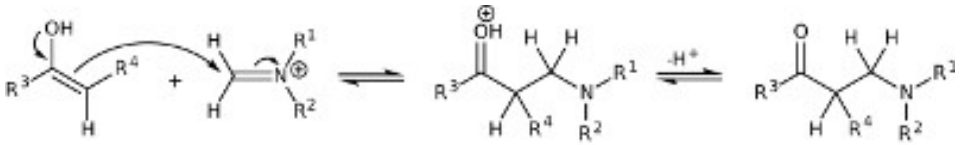
STEP II

The acid catalyses the conversion of acetone to its enolic tautomer



STEP III

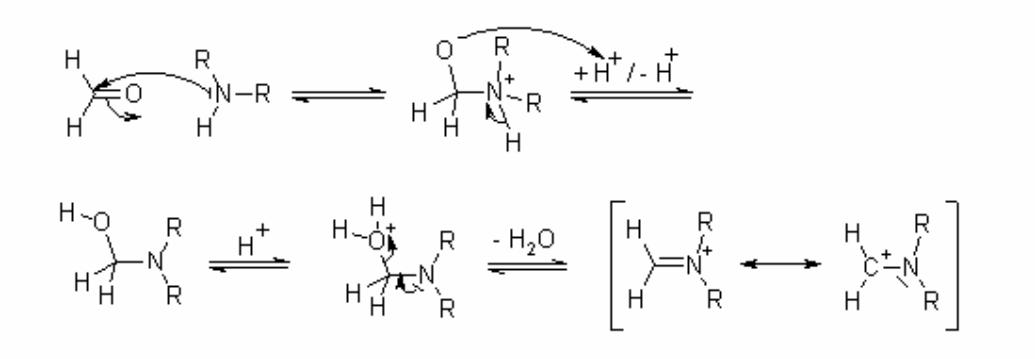
The enol then reacts with the electrophile and the resulting adduct loses a proton to form mannich base.



BASE CATALYSED REACTION:

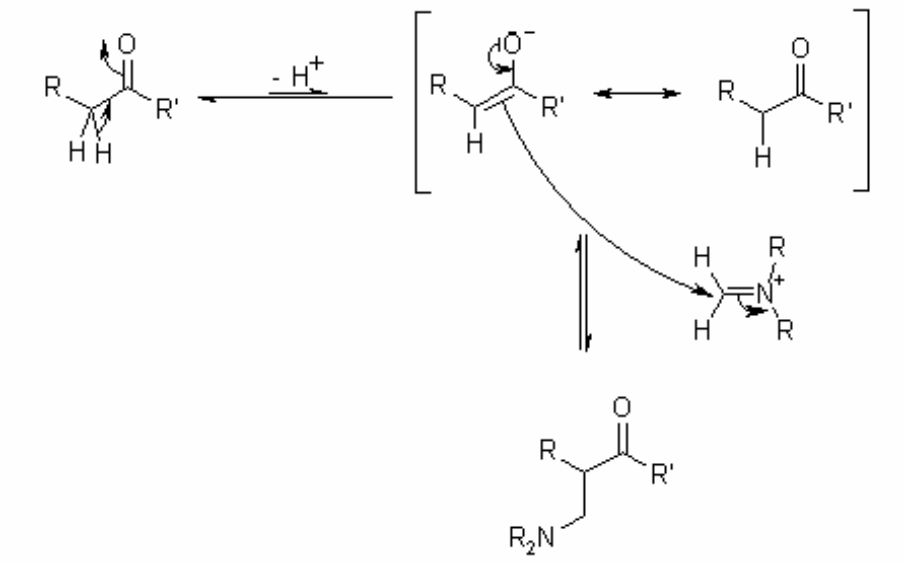
STEP I

The lone pair of electrons on nitrogen atom of the amine attacks the carbonyl carbon of formaldehyde to form an adduct.



STEP II

Base catalyses the conversion of acetone to carbanion and the carbanion reacts with the adduct to form the mannich base with the elimination of hydroxide ion.



SYNTHETIC AND ANALYTICAL WORKS

1. MATERIALS AND METHODS USED

All the amines used were obtained from Hi-media and Loba chem. The solvents and chemicals were procured from S.D Fine chem. Ltd., Fisher inorganics Ltd. All the compounds procured were purified and dried whenever necessary before use, following the standard methods.

Melting points were determined by using melting point apparatus, MR-VIS, Visual Melting Range Apparatus, Lab India. Purity of the compounds was routinely checked by TLC using plates coated with silica gel – G. Iodine vapours were used as the visualizing agents. Microwave synthesis was carried out using DAEWOO KOG-370A at Pharmaceutical Chemistry Laboratory, College of Pharmacy, SRIPMS, Coimbatore.

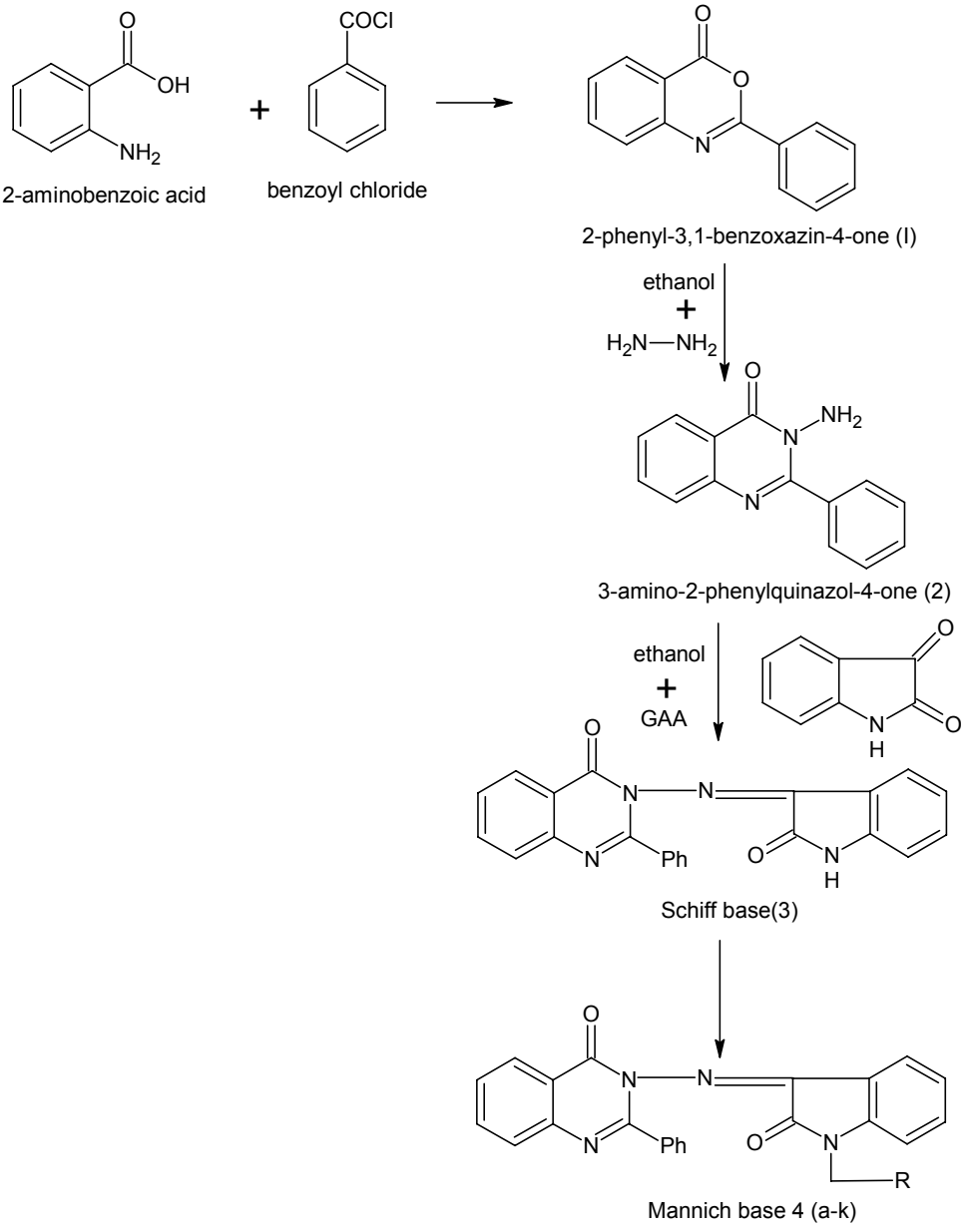
UV spectras were recorded on JASCO – V – 530. IR spectras were recorded on JASCO FT/IR – 410 at the Pharmaceutical Analytical Laboratory, College of Pharmacy, SRIPMS, Coimbatore.

Mass spectra and the PMR spectra were recorded at QUEST Research and Training Institute, Bangalore.

2. SCHEME

SCHEME – I

(CONVENTIONAL METHOD)



SCHEME II

(MICROWAVE SYNTHESIS)

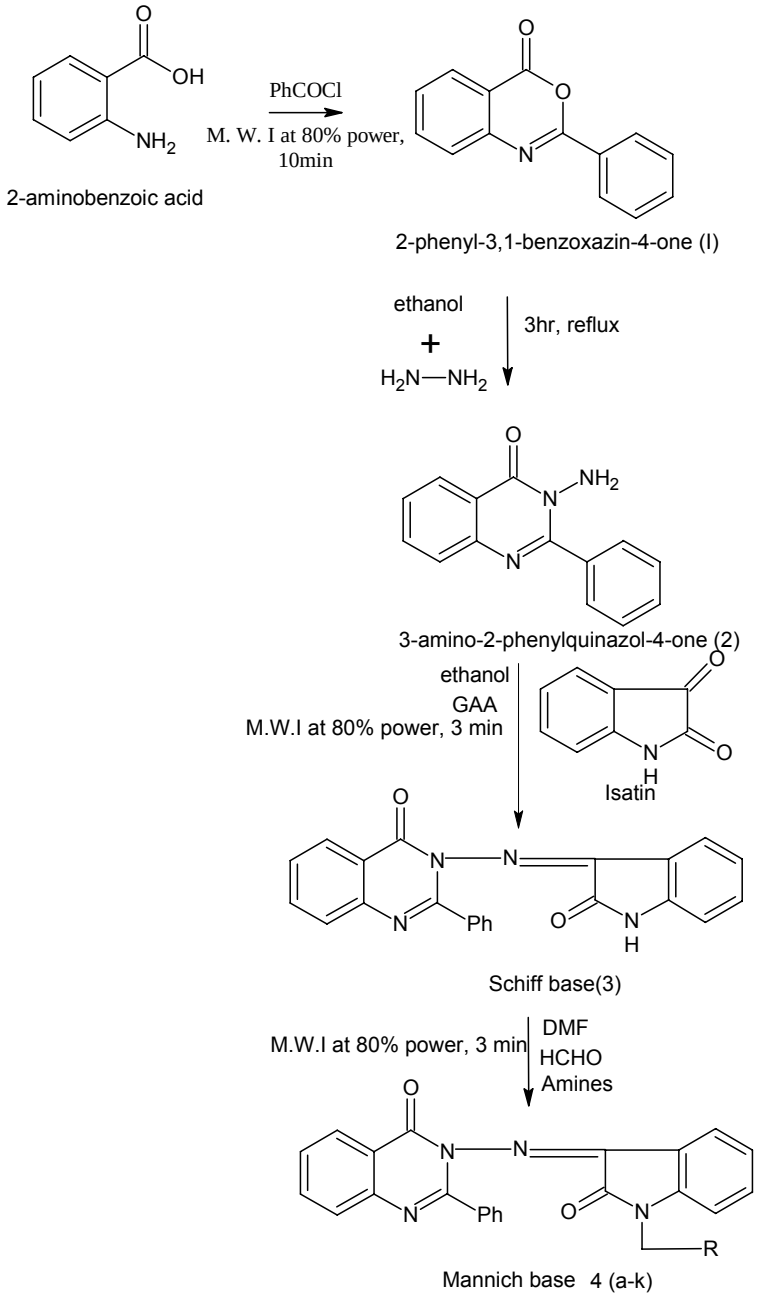
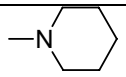
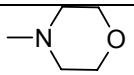
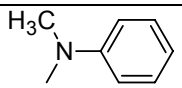
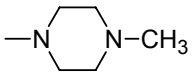
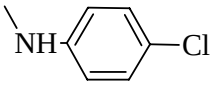
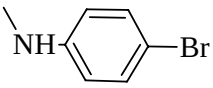
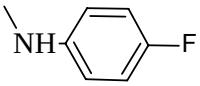
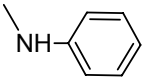


TABLE No. 1 : AMINES

AMINES	COMPOUND CODE	R

Piperidine	4 (a)	
Morpholine	4(b)	
N-Methyl Aniline	4(c)	
N-methylpiperazine	4(d)	
Dimethylamine	4(e)	-N(CH_3)$_2$
Diethylamine	4(f)	-N(C_2H_5)$_2$
Dipropylamine	4(g)	-N(C_3H_7)$_2$
4- chloroaniline	4(h)	
4- bromoaniline	4(i)	
4-fluoroaniline	4(j)	
Aniline	4(k)	

3. SYNTHETIC WORK

SCHEME I (CONVENTIONAL METHOD)

Step I

Synthesis of 2–phenyl–3,1–benzoxazin-4–one (1):[59]

To the solution of anthranilic acid (13.714g, 0.1 mol) dissolved in pyridine (60ml), benzoyl chloride (23.462g, 0.2mol) was added. The mixture was stirred for 30min followed by the treatment with 5% $NaHCO_3$ (15ml). The separated solid was recrystallised from ethanol, m.p.120^{0}C.

The purity of the compounds was determined by single spot on the TLC plates. The solvent system used was chloroform: methanol (7:3).

Step II

Synthesis of 3-amino-2-phenylquinazolin-4-one (2):[59]

A mixture of 2–phenyl–3,1–benzoxazin-4–one (11.15g, 0.05mol) and hydrazine hydrate (2.454g, 0.05mol) in ethanol was refluxed for 3 h and cooled. The separated solid was washed and recrystallised from ethanol (85%), m. p. 192-194^{0}C.

The purity of the compounds was determined by single spot on the TLC plates. The solvent system used was chloroform.

Step III

Synthesis of Schiff base (3):[60]

A mixture of 2 (2.13, 0.01mol) and isatin (1.441g, 0.01mol) in 10ml of ethanol and few drops of glacial acetic acid was refluxed for 1 h. The reaction mixture was kept at room temperature overnight. The yellow solid

thus separated out was washed with methanol and recrystallised from methanol, m. p. 270.2^{0}C .

The purity of the compounds was determined by single spot on the TLC plates. The solvent system used was chloroform: methanol (7:3).

Step IV

Synthesis of Mannich base (4):[60]

A mixture of 3 (Schiff base)(7.02g, 0.02mol) was dissolved in minimum quantity of DMF and slightly more amount of formaldehyde (0.02mol) and a primary or secondary amine (0.025) was added and stirred vigorously and heated on a water bath for 1 h and cooled and the product was washed and dried and recrystallised from methanol – dioxan mixture.

The purity of the compounds was determined by single spot on the TLC plates. The solvent system used was chloroform: methanol (7:3).

SCHEME II (MICROWAVE METHOD)

Step I

Synthesis of 2–phenyl–3,1–benzoxazin-4–one (1):[61]

To anthranilic acid (13.714, 0.1 mol), benzoyl chloride (23.462ml, 0.2mol) was added. The mixture was irradiated for 10min at 80% power, the solid so formed was washed with 5% $NaHCO_3$ (15ml). The separated solid was recrystallised from ethanol, m. p. 120^{0}C.

The purity of the compounds was determined by single spot on the TLC plates. The solvent system used was chloroform: methanol (7:3).

Step III

Synthesis of Schiff's base (3):[62]

A mixture of 2 (2.13, 0.01mol) and isatin (1.441g, 0.01mol) in ethanol and glacial acetic acid was irradiated at 80% power for 3min. The yellow solid thus separated out was washed with methanol and recrystallised from methanol, m. p.272^{0}C

The purity of the compounds was determined by single spot on the TLC plates. The solvent system used was chloroform: methanol (7:3).

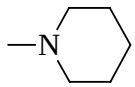
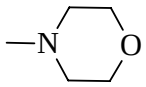
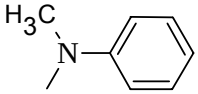
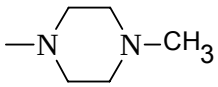
Step IV

Synthesis of mannich base (4):[62]

A mixture of 3 (Schiff base)(7.02g, 0.02mol) was dissolved in minimum quantity of DMF and slightly more amount of formaldehyde (0.02mol) and a primary or secondary amine (0.025) was added, this was then irradiated for 3min at 80% power and kept overnight. The product formed was washed in cold methanol, dried and recrystallised from methanol – dioxan mixture.

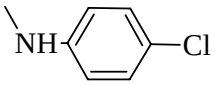
The purity of the compounds was determined by single spot on the TLC plates. The solvent system used was chloroform: methanol (7:3).

TABLE No. 2 : CHARACTERIZATION DATA OF COMPOUNDS 4 (a-d)

d	R	Molecular Formula	Mol.Wt	% Yield		Reaction Time		Melting Point (°C)	
				Conventional	MW	Conventional (h)	MW (min)		
		$C_{29}H_{27}N_5O_2$	477	72	89	1	3	251	
		$C_{28}H_{25}N_5O_3$	479	69	86	1	3	248	
		$C_{30}H_{24}N_5O_2$	499	67	82	1	3	263	
		$C_{29}H_{28}N_6O_2$	492	65	79	1	3	255	

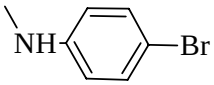
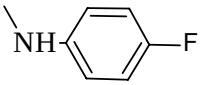
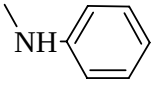
*Solvent system - chloroform: methanol (7:3)

CHARACTERIZATION DATA OF COMPOUNDS 4 (e-h)

d	R	Molecular Formula	Mol Wt	% Yield		Reaction Time		Melting Point (°C)	
				Conventional	MW	Conventional(h)	MW (min)		
	$-N(CH_3)_2$	$C_{25}H_{21}N_5O_2$	423	62	75	1	3	292	
	$-N(C_2H_5)_2$	$C_{27}H_{25}N_5O_2$	452	70	76	1	3	179	
	$-N(C_3H_7)_2$	$C_{29}H_{29}N_5O_2$	480	65	83	1	3	257	
		$C_{29}H_{20}ClN_5O_2$	521	65	77	1	3	286	

*Solvent system - chloroform: methanol (7:3)

CHARACTERIZATION DATA OF COMPOUNDS 4 (i-k)

d	R	Molecular Formula	Mol. Wt	% Yield		Reaction time		Melti Poi (°C	
				Conventional	MW	Conventional (h)	MW (min)		
		$C_{29}H_{20}BrN_5O_2$	566	64	77	1	3	268	
		$C_{29}H_{20}FN_5O_2$	505	60	74	1	3	210	
		$C_{29}H_{21}N_5O_2$	471	65	77	1	3	28(	

*Solvent system - chloroform: methanol (7:3)

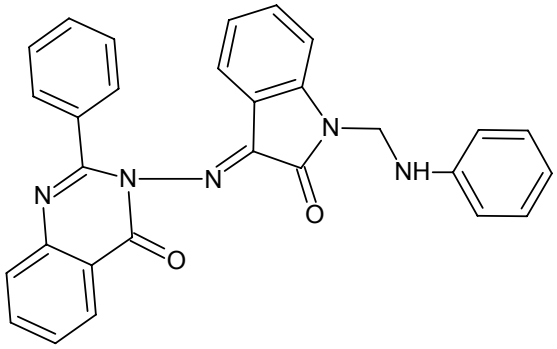
4. SPECTRAL CHARACTERIZATION STUDIES

Spectral data of prototype compounds

Chapter 5 Synthetic & Analytical Work

Structures of the mannich bases synthesized were established on the basis of chemical data, UV, IR, NMR and Mass spectral data. The purity of the compounds were established by single spot on TLC plate.

Compound – I : 4 k



Chemical name : 1-phenylamino-methyl-3-(2-phenyl-4-oxo-3-quinazolinylimino)-1,3-dihydro-indole-2-one

Molecular formula : $C_{29}H_{21}N_5O_2$

Molecular weight : 471.5

R_f value : 0.67

Percentage yield : 65% (Conventional method)
77% (Microwave method)

a) UV Spectrum

Solvent : methanol

λ_{max} : 310nm

b) **Infrared spectrum**:

The IR spectrum of the above compound showed characteristic absorption bands in the following region.[TABLE NO.:3]

S. No.	Type of Vibration	Wave No (cm^{-1})
1.	NH Stretch	3220.54
2.	Aliphatic CH Stretch	2926.45
3.	C=O of Isatin	1725.01
4.	C=O of Quinazolinone	1680.63
5.	C=N Stretch	1526.38
6.	C-N Stretch	1349.93

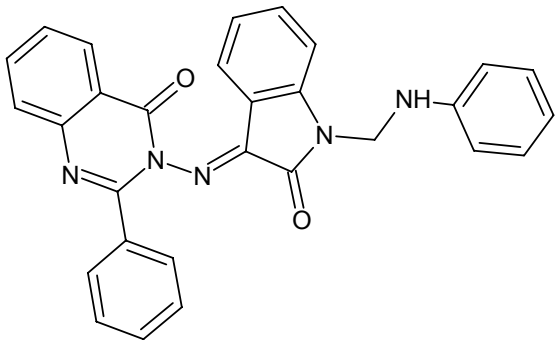
c) **PMR Spectrum (DMSO d_6):**

The Proton Magnetic resonance spectrum of the compound was in full agreement with the compounds molecular formula, with regard to proton count and also chemical shift.[TABLE NO. :4]

S. No	δ Values (ppm)	Type of protons	No of protons
1.	4.8	N- CH_2-N	2
2.	6.88-7.27	Aromatic protons and NH protons	19

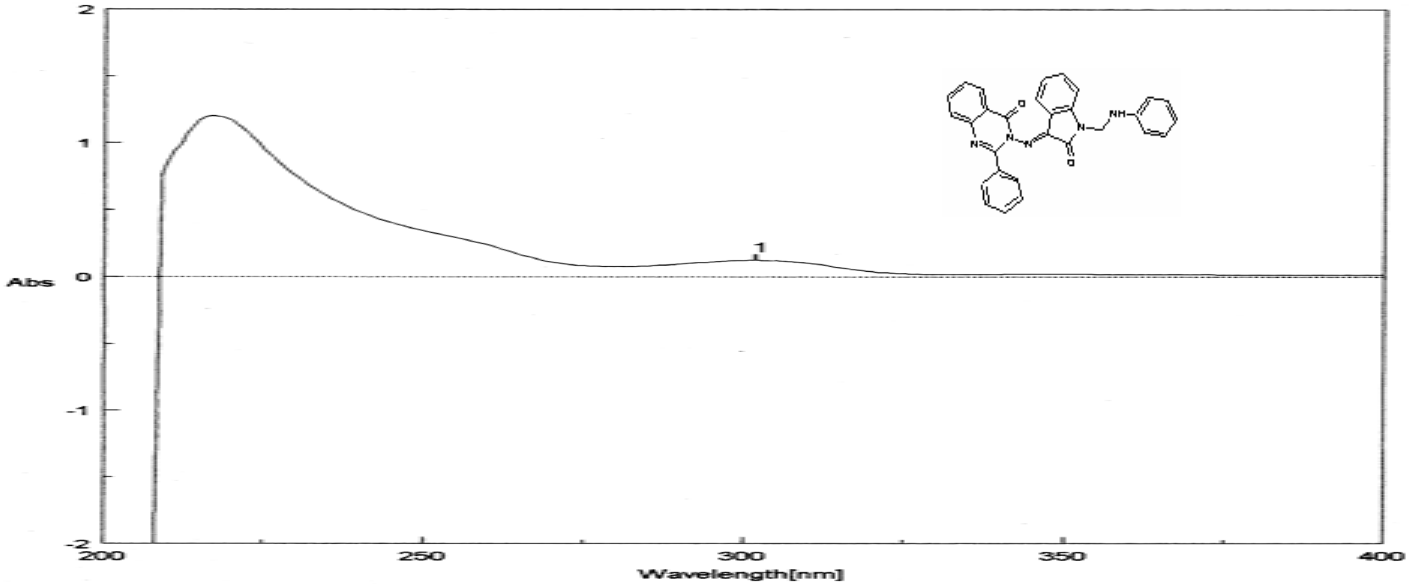
d) Mass Spectrum

(i) Molecular ion peak i. e., $(M+1)^+$ peak at 472.



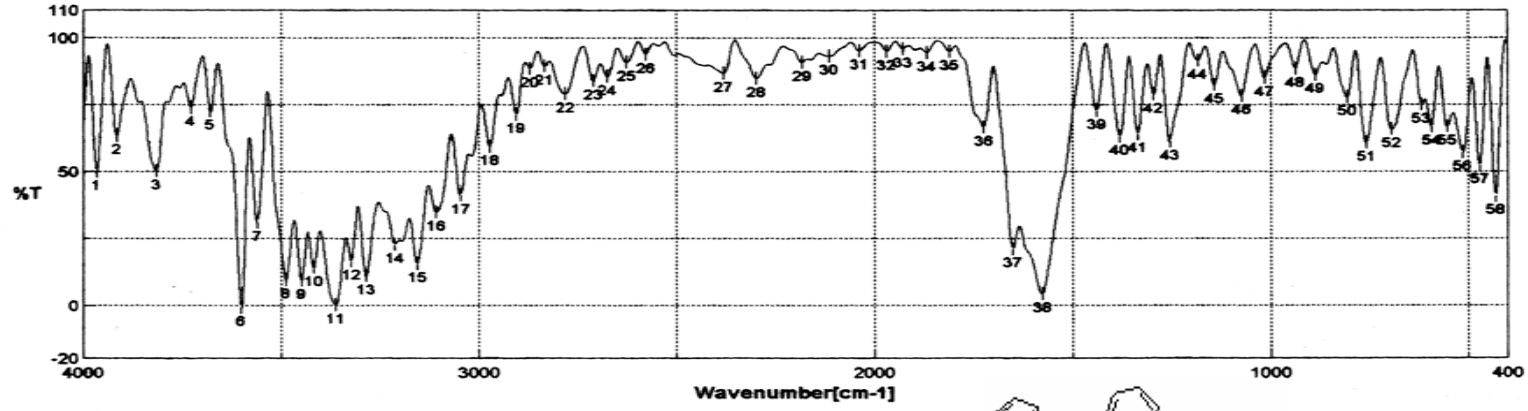
Different fragment ions are there.

UV SPECTRUM OF COMPOUND 4 k

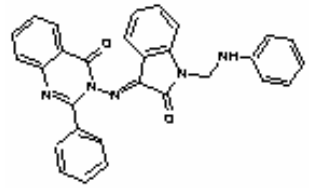


Date	03/12/2008 1:12PM
File name	4k
Model	V-530
Serial No.	B107260512
Band width	2.0 nm
Response	Medium
Measurement range	400 - 200 nm
Data pitch	1nm
Scanning speed	200nm/min
Sample ID	36
No. of cycle	1
Sample name	
Operator	pharm analysis
Comment	

IR SPECTRUM 4 k

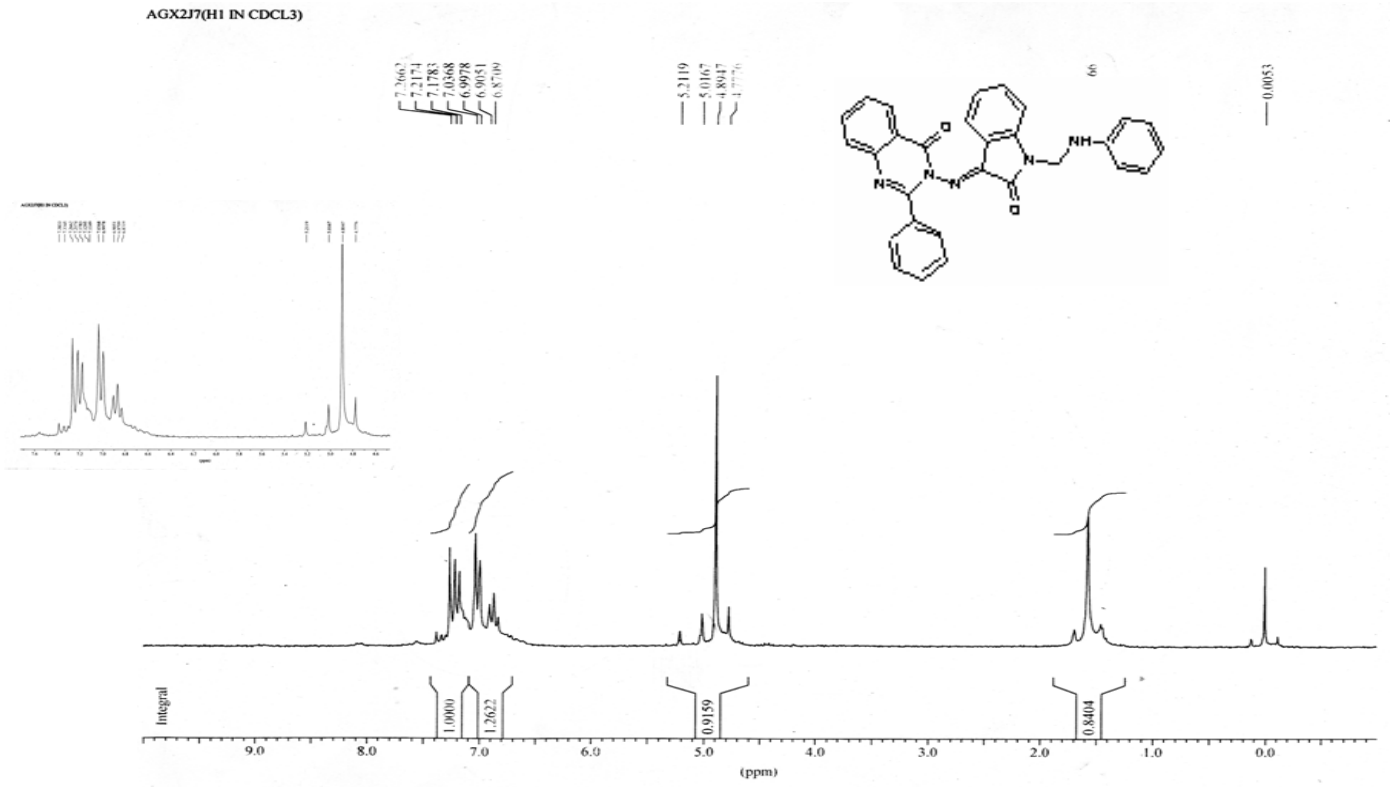


Accumulation	40	Resolution	4 cm-1
Zero Filling	ON	Apodization	Cosine
Gain	32	Scanning Speed	2 mm/sec
Date/Time	1/24/2009 0:37PM	Update	1/27/2009 9:40AM
Operator	C.Geetha		
File Name	IV k		
Sample Name	3		
Comment			



No.	cm-1	%T	No.	cm-1	%T	No.	cm-1	%T	No.	cm-1	%T	No.	cm-1	%T
1	3965.89	49.8853	2	3915.75	63.387	3	3817.4	50.2598	4	3728.69	74.0639	5	3678.55	72.4101
6	3601.41	-0.712453	7	3560.91	30.9371	8	3486.6	9.44458	9	3450.03	9.28937	10	3418.21	14.0809
11	3363.25	0.127302	12	3323.71	16.5742	13	3286.11	10.9103	14	3211.86	22.8725	15	3155.94	15.6373
16	3108.69	34.7331	17	3047.94	41.0255	18	2973.7	59.2482	19	2907.16	71.4057	20	2871.49	88.4792
21	2833.88	89.2699	22	2781.81	78.9019	23	2710.46	83.7209	24	2674.78	85.3792	25	2626.57	90.7718
26	2578.36	93.7787	27	2381.66	86.5811	28	2298.73	84.7671	29	2184.95	90.844	30	2116.49	93.1166
31	2039.35	95.1839	32	1968.96	94.9718	33	1928.47	95.927	34	1867.72	94.4488	35	1810.83	94.7688
36	1725.01	66.6224	37	1650.77	21.1143	38	1577.49	4.19241	39	1439.6	72.8318	40	1380.78	83.1823
41	1335.46	84.1147	42	1294.97	78.7945	43	1254.47	81.2061	44	1183.11	91.4382	45	1140.69	82.2775
46	1073.19	78.2464	47	1015.34	85.0229	48	937.235	88.4509	49	886.131	86.1718	50	805.135	77.7933
51	756.923	60.6898	52	693.284	85.6763	53	618.074	74.9982	54	593.004	88.687	55	553.47	88.6393
56	513.936	57.19	57	471.51	52.3044	58	431.012	40.8602						

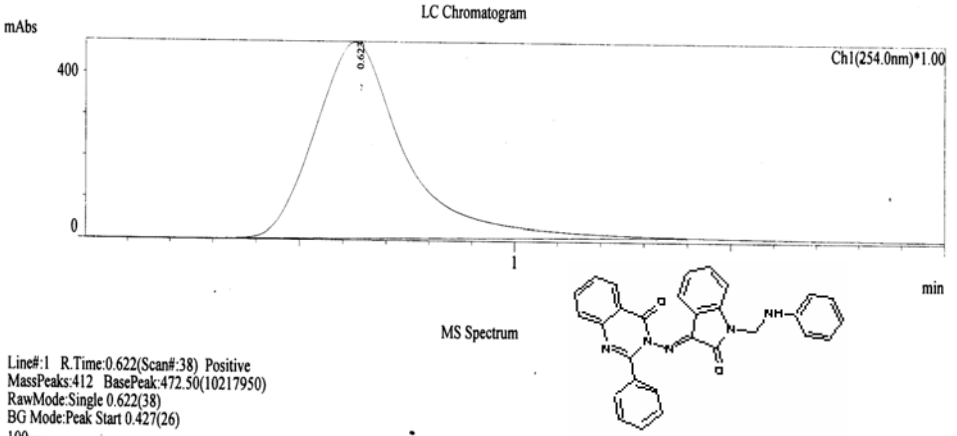
PMR SPECTRUM OF 4 k


AGX2J7(H1 IN CDCL3)
7.2663
7.2174
7.1783
7.0368
6.9978
6.9051
5.2119
5.0167
4.8047
0.0053
NH
Integral
1.0000
1.2622
0.9159
0.8404
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
(ppm)

MASS SPECTRUM OF 4 k

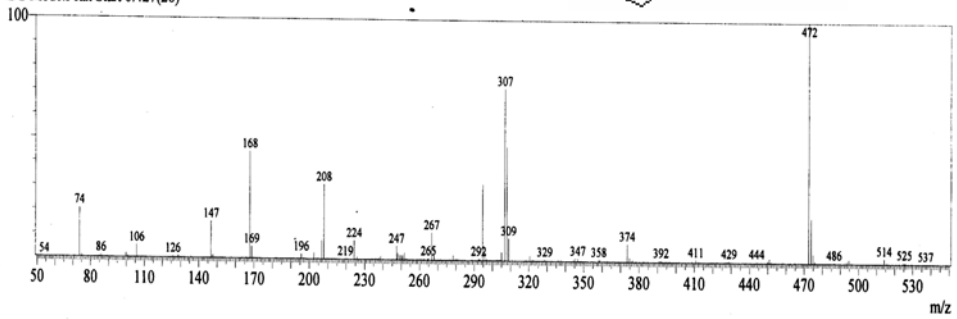
LCMS-2010A DATA REPORT
SHIMADZU

User : Admin
Sample : JXR2A7
Inj. Volume : 5.000
Data Name : C:\LCMSsolution\User\Data\JXR2A7-APCI-POS1.qld
Method Name : C:\LCMSsolution\User\Method\Copy of JAY-4-APCI.qlm



MS Spectrum

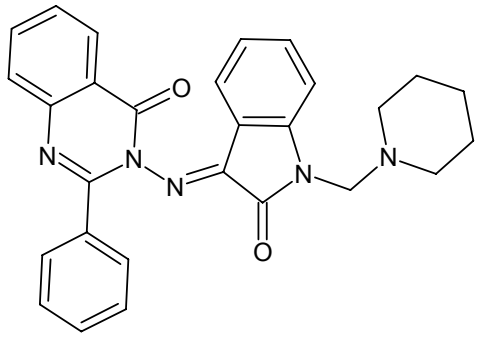
Line#:1 R.Time:0.622(Scan#:38) Positive
MassPeaks:412 BasePeak:472.50(10217950)
RawMode:Single 0.622(38)
BG Mode:Peak Start 0.427(26)



MS Peak Table

Peak#	R.Time	I.Time	F.Time	Area	Height	A/H	Mark	%Total	Name	Base m/z	Base Int.
1	0.622	0.427	0.943	740845070	75336787	9.83		100.00		472.50	10217950
				740845070	75336787			100.00			

Compound – II : 4 a



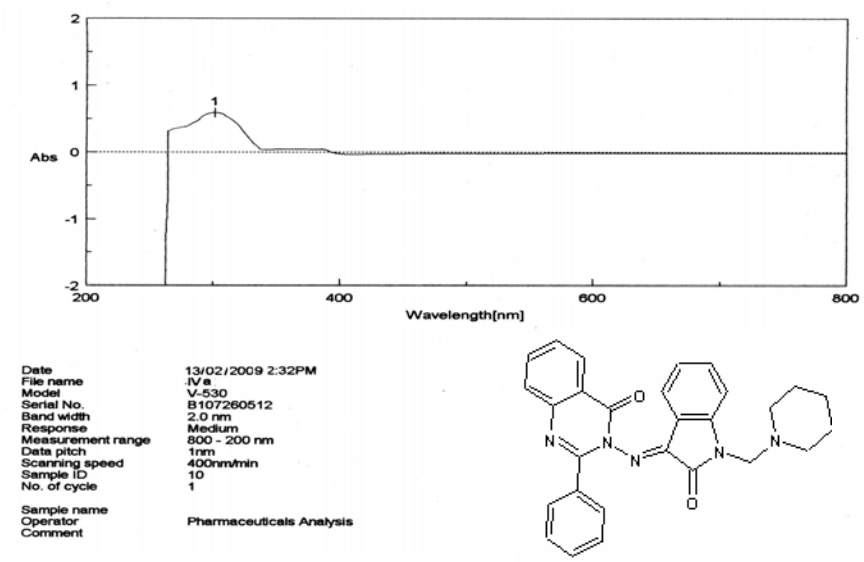
Chemical name : 1-Piperidino-methyl-3-(2-phenyl-4-oxo-3-quinazolinylimino)-1,3-dihydro-indole-2-one

Molecular formula : $C_{28}H_{25}N_5O_2$

a) UV Spectrum

Solvent : methanol

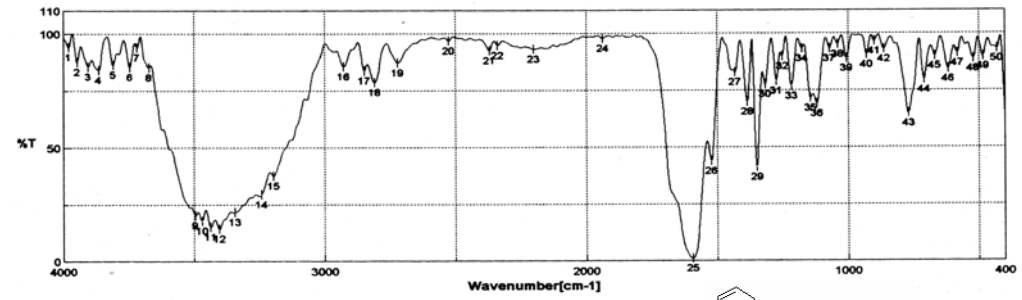
λ_{max} : 314nm



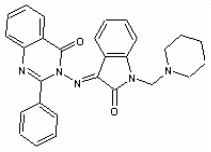
b) **Infrared spectrum**:

The IR spectrum of the above compound showed characteristic absorption bands in the following region.[TABLE NO.: 5]

S. No.	Type of Vibration	Wave No (cm^{-1})
1.	Aromatic C-H Stretch	3110.36
2.	Aliphatic CH Stretch	2912.30
3.	C=O of Quinazolinone	1655.78
4.	C=N Stretch	1574.27
5.	C-N Stretch	1340.96
6.	Aromatic C-H bend	707.74

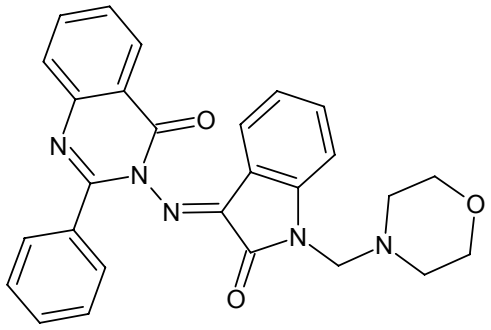


Accumulation	40	Resolution	4 cm-1
Zero Filling	ON	Apodization	Cosine
Gain	4	Scanning Speed	2 mm/sec
Date/Time	2/10/2009 2:43PM	Update	2/10/2009 2:55PM
Operator	C.Geetha		
File Name	4a		
Sample Name	4A		
Comment			



No.	cm-1	%T	No.	cm-1	%T	No.	cm-1	%T	No.	cm-1	%T	No.	cm-1	%T
1	3980.36	94.0958	2	3947.57	87.5384	3	3904.18	85.6685	4	3865.61	84.2262	5	3810.85	86.3813
6	3746.05	85.4166	7	3718.08	93.8969	8	3673.73	85.1237	9	3495.35	20.3627	10	3470.28	17.9804
11	3437.49	15.1705	12	3404.71	14.3898	13	3345.89	21.6684	14	3243.68	29.3855	15	3110.43	37.7034
16	2912.34	85.5696	17	2850.27	83.852	18	2809.78	78.6912	19	2721.07	87.1855	20	2527.26	96.8195
21	2370.09	92.5203	22	2338.27	94.8515	23	2201.34	93.1756	24	1937.15	97.8704	25	1655.78	1.2487
26	1574.27	43.9791	27	1432.85	82.8928	28	1385.6	89.8689	29	1340.96	41.2762	30	1318.11	77.5946
31	1275.88	79.0131	32	1251.58	89.8475	33	1216.86	76.9335	34	1176.36	93.4151	35	1142.82	71.6034
36	1118.51	89.1887	37	1089.33	93.3618	38	1039.44	95.1852	39	1006.86	89.1139	40	928.557	90.6267
41	899.63	96.4884	42	862.989	93.0873	43	767.53	64.872	44	707.747	79.727	45	667.25	90.0617
46	617.109	84.414	47	581.433	91.2487	48	521.65	88.8532	49	485.009	89.8516	50	431.012	93.2406

Compound – III : 4 b



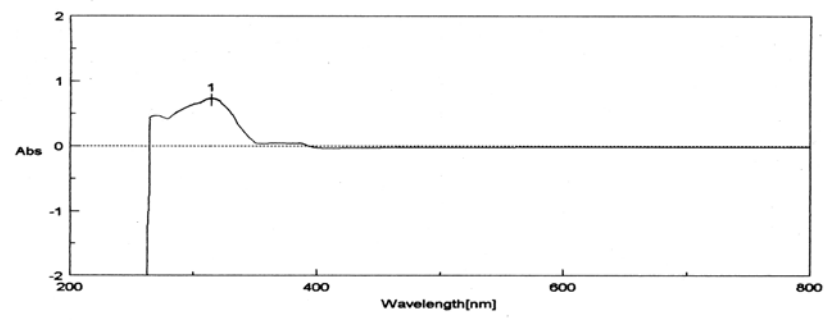
Chemical name : 1-Morpholino-methyl-3-(2-phenyl-4-oxo-3-quinazolinylimino)-1,3-dihydro-indole-2-one

Molecular formula : $C_{28}H_{25}N_5O_3$

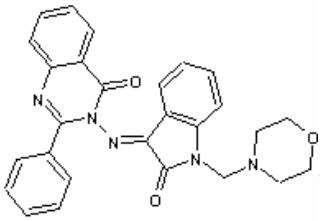
a) UV Spectrum

Solvent : methanol

λ_{max} : 308nm



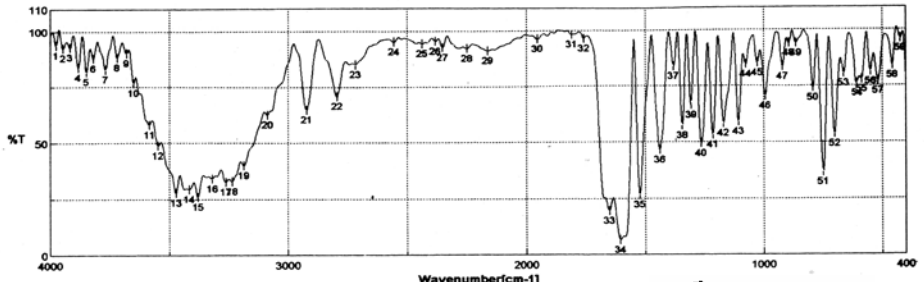
Date	13/02/2009 2:52PM
File name	IV b
Model	V-530
Serial No.	B107260512
Band width	2.0 nm
Response	Medium
Measurement range	800 - 200 nm
Data pitch	1nm
Scanning speed	400nm/min
Sample ID	10
No. of cycle	1
Sample name	
Operator	Pharmaceuticals Analysis
Comment	



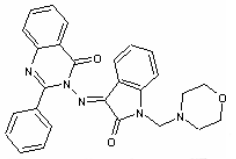
b) Infrared spectrum:

The IR spectrum of the above compound showed characteristic absorption bands in the following region.[TABLE NO.: 6]

S.No.	Type of Vibration	Wave No (cm^{-1})
1.	Aromatic CH Stretch	3082.65
2.	Aliphatic CH Stretch	2971.77
3.	C=O of Quinazolinone	1651.73
4.	C=N Stretch	1522.52
5.	C-N Stretch	1343.18
6.	C-H Bend	698.105

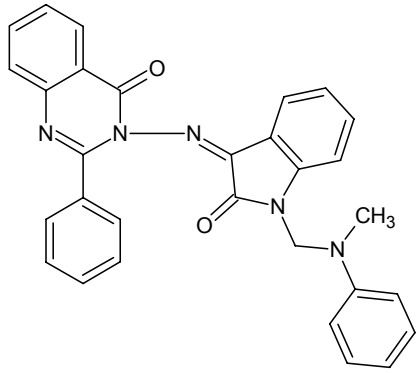


Accumulation	40	Resolution	4 cm-1
Zero Filling	ON	Apodization	Cosine
Gain	8	Scanning Speed	2 mm/sec
Date/Time	2/10/2009 2:56PM	Update	2/10/2009 3:00PM
Operator	C.Geetha		
File Name	4b		
Sample Name	4b		
Comment			



No.	cm-1	%T	No.	cm-1	%T	No.	cm-1	%T	No.	cm-1	%T	No.	cm-1	%T
1	3976.5	93.6549	2	3946.61	92.4601	3	3917.66	92.8865	4	3882.97	93.8927	5	3849.22	91.7998
6	3821.26	87.8833	7	3770.15	82.8218	8	3720.98	88.31	9	3682.41	90.3735	10	3652.52	78.7183
11	3585.02	58.0459	12	3548.38	48.835	13	3472.2	27.8385	14	3416.28	29.5005	15	3379.64	25.9544
16	3319.96	34.2568	17	3262	32.8977	18	3235.97	32.9374	19	3185.83	39.9887	20	3087.48	62.4899
21	2923.56	84.7221	22	2795.31	70.7188	23	2717.21	85.2936	24	2556.18	95.298	25	2438.55	94.5082
26	2362.62	95.524	27	2351.77	92.7676	28	2251.49	92.3769	29	2164.7	91.2703	30	1955.47	96.3037
31	1811.79	98.2341	32	1760.69	96.2786	33	1651.73	19.693	34	1604.48	6.64589	35	1522.52	26.8856
36	1439.6	46.8109	37	1380.78	63.8176	38	1343.18	57.2934	39	1307.5	66.5684	40	1264.11	49.4071
41	1213.97	53.3325	42	1169.85	58.3663	43	1105.98	59.1214	44	1074.16	84.4922	45	1025.94	85.1765
46	993.16	70.8054	47	918.914	83.5411	48	882.88	93.8896	49	862.986	93.9125	50	790.671	74.1654
51	746.317	36.8712	52	698.105	53.7259	53	662.428	80.5091	54	606.503	76.1123	55	586.254	77.9263
56	548.649	81.4163	57	517.793	77.1194	58	458.011	84.0574	59	423.298	96.0289			

Compound – IV : 4 c



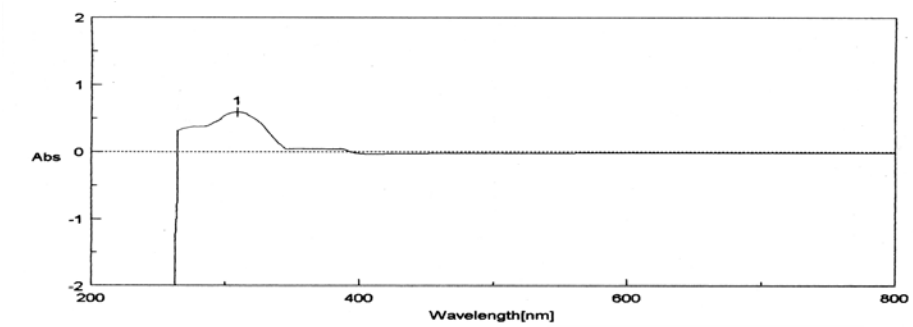
Chemical name : 1-(N-methylphenylamino)-methyl-3-(2-phenyl-4-oxo-3-quinazolinylimino)-1,3-dihydro-indole-2-one

Molecular formula : $C_{30}H_{23}N_5O_2$

a) UV Spectrum

Solvent : Methanol

λ_{max} : 313nm



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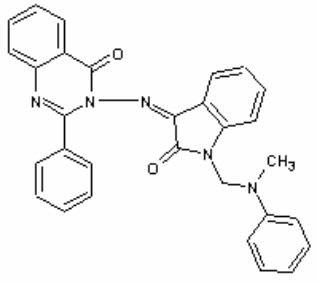
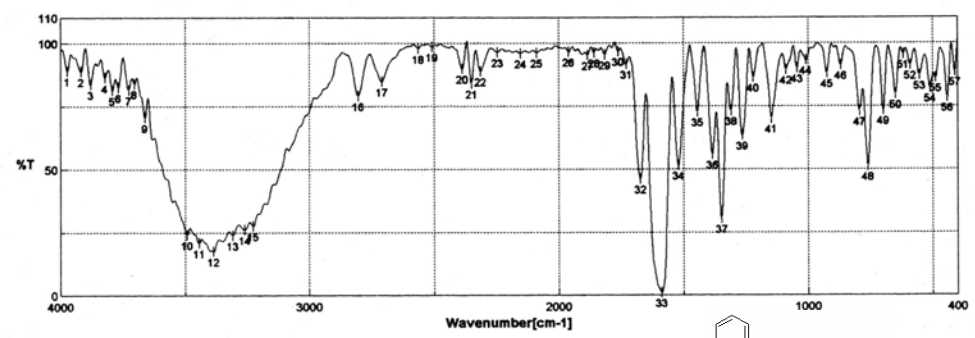
Measurement range	800 - 200 nm
Data pitch	1nm
Scanning speed	400nm/min
Sample ID	10
No. of cycle	1
Sample name	
Operator	Pharmaceuticals Analysis
Comment	



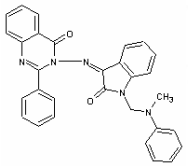
b) **Infrared spectrum**:

The IR spectrum of the above compound showed characteristic absorption bands in the following region.[TABLE NO.: 7]

S.No.	Type of Vibration	Wave No (cm^{-1})
1.	C=O of Quinazolinone	1673.91
2.	C=N Stretch	1589.06
3.	C-N Stretch	1347.03
5.	C-H Bend	698.10

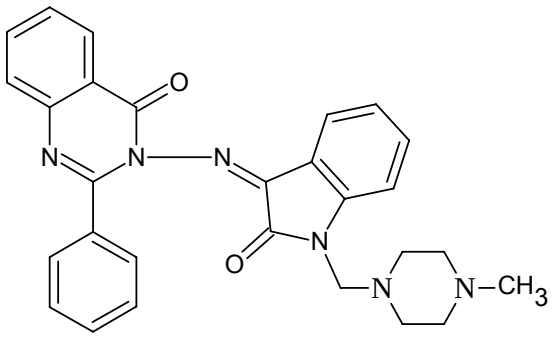


Accumulation	40	Resolution	4 cm-1
Zero Filling	ON	Apodization	Cosine
Gain	8	Scanning Speed	2 mm/sec
Date/Time	2/11/2009 3:32PM	Update	2/11/2009 3:36PM
Operator	C.Geetha		
File Name	4c		
Sample Name	4c		
Comment			



No.	cm-1	%T	No.	cm-1	%T	No.	cm-1	%T	No.	cm-1	%T	No.	cm-1	%T
1	3972.64	88.998	2	3918.64	88.7929	3	3879.11	83.6772	4	3821.26	86.4223	5	3791.37	81.2322
6	3767.26	82.5264	7	3726.76	81.5697	8	3702.66	83.9758	9	3661.19	70.5728	10	3493.42	24.2724
11	3445.21	20.9309	12	3387.35	17.6723	13	3310.21	24.0408	14	3262	28.2238	15	3227.29	27.6016
16	2806.88	79.14	17	2711.42	84.7428	18	2564.86	97.8578	19	2508.94	98.5452	20	2388.41	89.8322
21	2350.8	84.0268	22	2314.16	88.7695	23	2246.66	96.4706	24	2154.1	96.0558	25	2086.53	96.214
26	1960.29	96.5157	27	1884.11	95.212	28	1858.08	96.2361	29	1815.65	95.4458	30	1761.85	96.7393
31	1729.83	91.6208	32	1673.91	46.1344	33	1589.06	1.27351	34	1520.6	51.5559	35	1444.42	72.7497
36	1383.68	56.0157	37	1347.03	30.4901	38	1309.43	73.2827	39	1265.07	63.4119	40	1219.76	86.5083
41	1146.47	70.1656	42	1087.66	86.5384	43	1044.26	90.1722	44	1007.62	93.244	45	924.7	88.0462
46	869.738	91.231	47	794.528	73.0955	48	759.816	51.3369	49	698.105	73.3395	50	649.893	79.7016
51	619.038	95.5963	52	590.111	91.2571	53	553.47	87.2404	54	510.08	82.1752	55	488.866	86.1331
56	441.619	78.4307	57	411.728	88.5671									

Compound – V : 4 d



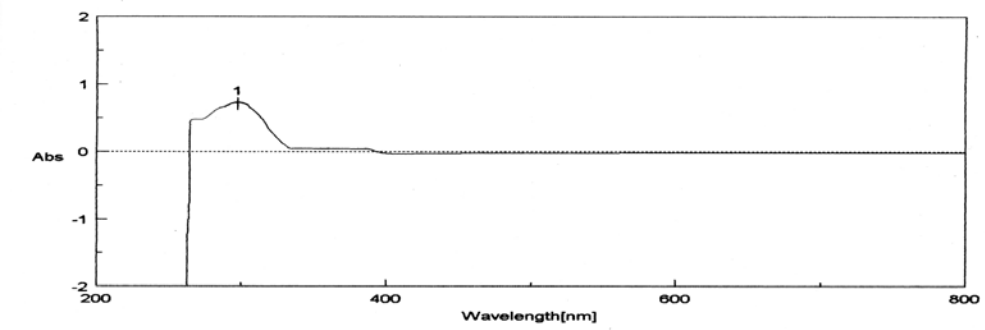
Chemical name : 1-(N-methylpiperazino)-methyl-3-(2-phenyl-4-oxo-3-quinazolinylimino)-1,3-dihydro-indole-2-one

Molecular formula : $C_{28}H_{26}N_6O_2$

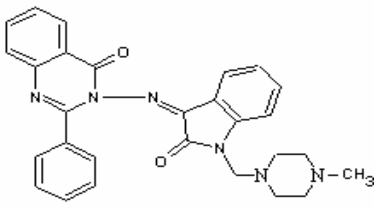
a) UV Spectrum

Solvent : methanol

λ_{max} : 307nm



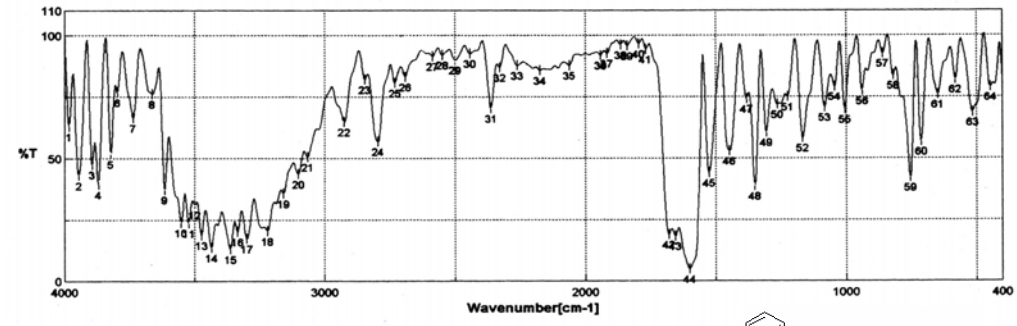
Date	13/02/2009 3:02PM
File name	IV d
Model	V-530
Serial No.	B107260512
Band width	2.0 nm
Response	Medium
Measurement range	800 - 200 nm
Data pitch	1nm
Scanning speed	400nm/min
Sample ID	10
No. of cycle	1
Sample name	
Operator	Pharmaceuticals Analysis
Comment	



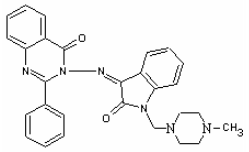
b) **Infrared spectrum**:

The IR spectrum of the above compound showed characteristic absorption bands in the following region.[TABLE NO. :8]

S.No.	Type of Vibration	Wave No (cm^{-1})
1.	Aromatic C-H Stretch	3102.9
2.	Aliphatic CH Stretch	2926.45
3.	C=O of Quinazolinone	1680.66
4.	C=N Stretch	1526.38
5.	C-N Stretch	1349.93
6.	Aromatic C-H bend	709.676

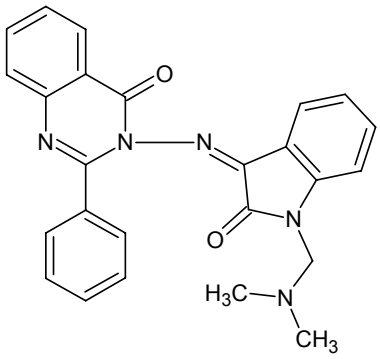


Accumulation	40	Resolution	4 cm-1
Zero Filling	ON	Apodization	Cosine
Gain	16	Scanning Speed	2 mm/sec
Date/Time	2/10/2009 3:00PM	Update	2/10/2009 3:06PM
Operator	C.Geetha		
File Name	4d		
Sample Name	4d		
Comment			



No.	cm-1	%T	No.	cm-1	%T	No.	cm-1	%T	No.	cm-1	%T	No.	cm-1	%T
1	3983.25	82.9993	2	3945.64	43.1319	3	3894.54	47.4879	4	3870.43	39.5054	5	3823.19	51.924
6	3797.15	76.8779	7	3736.4	66.4976	8	3663.12	78.2294	9	3614.91	37.4848	10	3552.24	24.0328
11	3523.31	23.8615	12	3500.17	31.2644	13	3474.13	18.848	14	3436.53	13.9067	15	3384.21	13.1733
16	3336.25	20.306	17	3300.57	17.4739	18	3220.54	20.8286	19	3158.83	35.8261	20	3102.9	43.8091
21	3067.23	50.7137	22	2926.45	64.7844	23	2847.38	82.0907	24	2797.24	56.8898	25	2730.71	80.682
26	2691.18	83.2428	27	2587.04	91.5348	28	2549.43	92.0095	29	2500.26	90.0499	30	2443.37	92.632
31	2362.37	70.341	32	2328.62	87.0996	33	2261.13	87.8522	34	2175.31	85.8369	35	2063.46	87.8728
36	1941.97	91.851	37	1915.93	92.6788	38	1864.83	96.2749	39	1838.79	95.7702	40	1795.4	96.6132
41	1768.4	94.2967	42	1680.66	19.0392	43	1655.59	18.4828	44	1600.63	5.15001	45	1526.38	44.0299
46	1447.31	53.0494	47	1382.71	74.2178	48	1349.93	38.921	49	1307.5	80.5235	50	1265.07	71.9415
51	1225.54	75.004	52	1166.72	58.2707	53	1080.91	70.7744	54	1043.3	79.1993	55	1004.73	70.0125
56	938.199	77.562	57	859.132	92.6787	58	818.634	83.6875	59	751.138	42.3752	60	709.676	56.8785

Compound – VI : 4 e



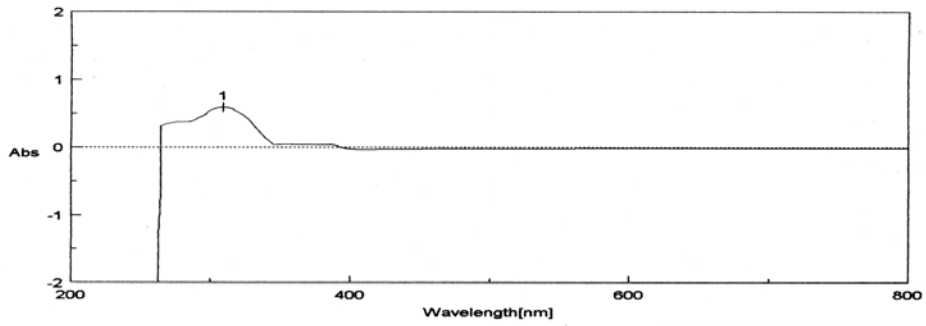
Chemical name : 1-(N,N-dimethylamino)- methyl-3-(2-phenyl-4-oxo-3-quinazolinylimino)-1,3-dihydro-indole-2-one

Molecular formula : $C_{25}H_{21}N_5O_2$

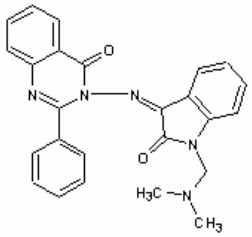
a) UV Spectrum

Solvent : methanol

λ_{max} : 311nm



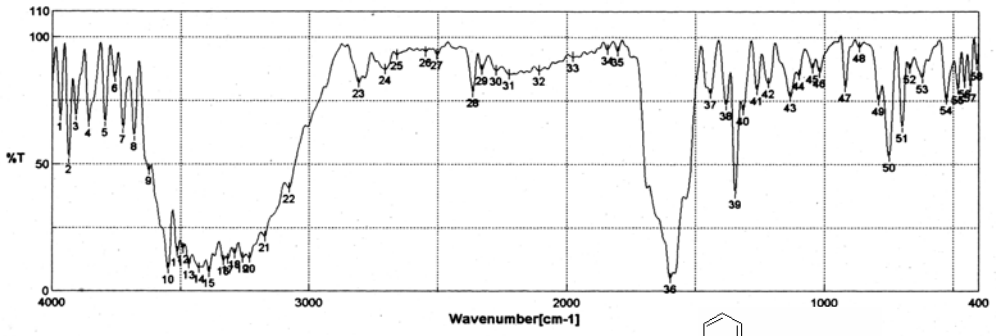
Date	13/02/2009 3:12 PM
File name	IV e
Model	V-530
Serial No.	B107260512
Band width	2.0 nm
Response	Medium
Measurement range	800 - 200 nm
Data pitch	1nm
Scanning speed	400nm/min
Sample ID	10
No. of cycle	1
Sample name	
Operator	Pharmaceuticals Analysis
Comment	



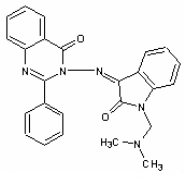
b) **Infrared spectrum**:

The IR spectrum of the above compound showed characteristic absorption bands in the following region.[TABLE NO.:9]

S.No.	Type of Vibration	Wave No (cm^{-1})
1.	Aromatic CH Stretch	3078.8
2.	C=N Stretch	1441.31
3.	C-N Stretch	1346.07
4.	Aromatic CH Bend	696.177

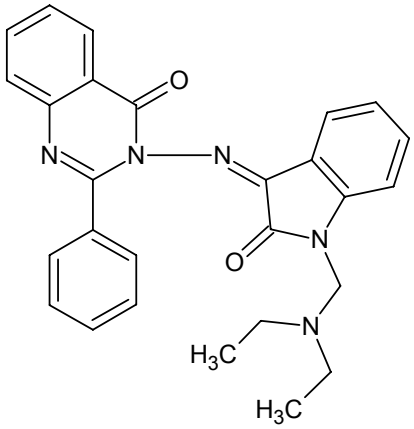


Accumulation	40	Resolution	4 cm-1
Zero Filling	ON	Apodization	Cosine
Gain	16	Scanning Speed	2 mm/sec
Date/Time	2/13/2009 1:01PM	Update	2/27/2009 6:04PM
Operator	C.Geetha		
File Name	IV e		
Sample Name	4i		
Comment			



No.	cm-1	%T	No.	cm-1	%T	No.	cm-1	%T	No.	cm-1	%T	No.	cm-1	%T
1	3968.78	69.0163	2	3935.04	52.2089	3	3907.07	69.1638	4	3858.86	66.4646	5	3794.26	66.6714
6	3757.62	84.13	7	3724.83	64.082	8	3681.44	61.2825	9	3624.55	47.7345	10	3549.34	8.95467
11	3513.67	15.5781	12	3491.49	16.8789	13	3467.38	10.7186	14	3427.85	9.23815	15	3389.28	7.4966
16	3334.32	12.217	17	3316	12.7417	18	3289.96	14.9242	19	3258.14	13.1842	20	3233.07	13.129
21	3173.29	21.6213	22	3078.8	40.6067	23	2809.78	82.1554	24	2705.64	87.3703	25	2660.32	93.1633
26	2548.47	94.4163	27	2504.11	93.3524	28	2365.26	78.5826	29	2330.55	87.3033	30	2274.63	87.0103
31	2223.52	85.4896	32	2108.78	86.9564	33	1975.71	92.2177	34	1842.65	95.126	35	1802.15	94.6276
36	1598.7	5.34188	37	1441.53	77.7906	38	1381.75	73.4668	39	1346.07	38.6673	40	1316.18	71.4686
41	1282.18	79.3763	42	1217.83	82.1402	43	1132.01	78.617	44	1099.23	85.1008	45	1046.19	87.9233
46	1018.23	86.2192	47	918.914	80.4833	48	863.953	96.2363	49	789.707	75.3312	50	748.245	53.0376
51	696.177	64.6815	52	668.214	87.7565	53	620.002	84.0727	54	526.471	75.547	55	482.117	79.7433
56	456.082	82.0915	57	432.941	90.5724									

Compound – VII : 4 f



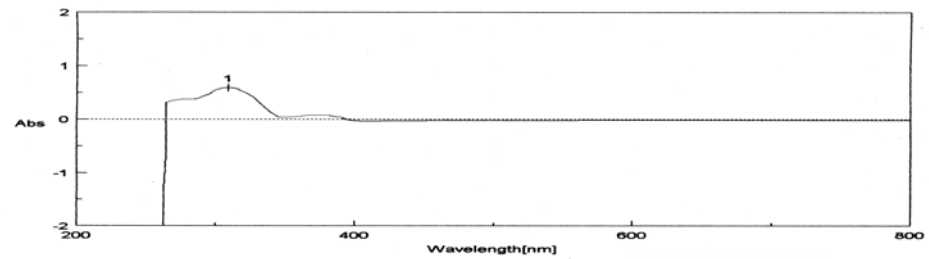
Chemical name : 1-(N,N-diethylamino)-methyl-3-(2-phenyl-4-oxo-3-quinazolinylimino)-1,3-dihydro-indole-2-one

Molecular formula : $C_{27}H_{25}N_5O_2$

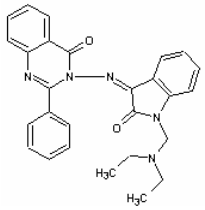
a) UV Spectrum

Solvent : methanol

λ_{max} : 317nm



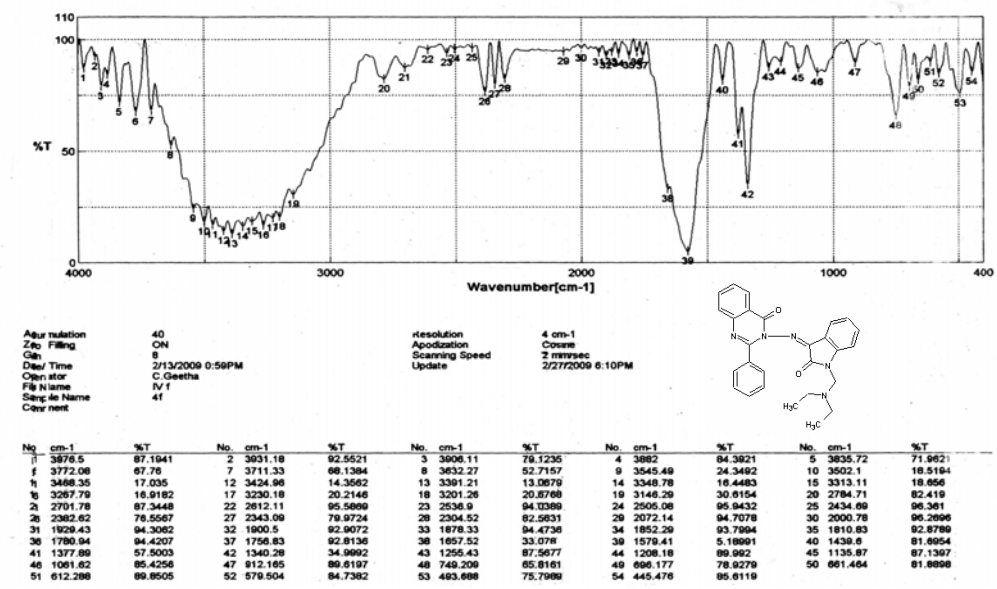
Date	13/02/2009 3:20PM
File name	IV f
Model	V-530
Serial No.	B107260512
Band width	2.0 nm
Response	Medium
Measurement range	800 - 200 nm
Data pitch	1nm
Scanning speed	400nm/min
Sample ID	10
No. of cycle	1
Sample name	
Operator	
Comment	Pharmaceuticals Analysis



b) **Infrared spectrum**:

The IR spectrum of the above compound showed characteristic absorption bands in the following region.[TABLE NO.:10]

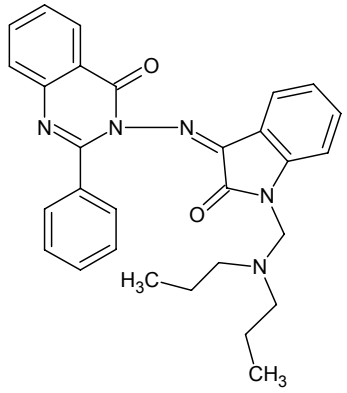
S. No.	Type of Vibration	Wave No (cm^{-1})
1.	Aromatic CH Stretch	3146.29
2.	C=O of Isatin	1756.83
3.	C=O of Quinazolinone	1657.52
4.	C=N Stretch	1439.6
5.	C-N Stretch	1340.28
6.	Aromatic CH Bend	696.177



Accumulation	40	Resolution	4 cm-1
Zero Filling	ON	Apodization	Cosine
Gain	8	Scanning Speed	2 mm/sec
Date/ Time	2/13/2009 0:59PM	Update	2/27/2009 6:10PM
Operator	C.Geetha		
File Name	IV f		
Sample Name	4f		
Comment			

No	cm-1	%T	No	cm-1	%T	No	cm-1	%T	No	cm-1	%T	No	cm-1	%T
1	3876.5	87.1941	2	3931.18	92.5521	3	3906.11	79.1235	4	3882	84.3821	5	3835.72	71.9621
f	3772.08	87.76	7	3711.33	88.1384	8	3632.27	52.7157	9	3545.49	24.3492	10	3502.1	18.5194
h	3468.35	17.035	12	3424.98	14.3562	13	3391.21	13.0879	14	3348.78	16.4483	15	3313.11	18.656
1g	3267.79	16.9182	17	3230.18	20.2146	18	3201.26	20.6768	19	3146.29	30.6154	20	2784.71	82.419
2h	2701.78	87.3448	22	2612.11	95.5899	23	2536.9	94.0369	24	2505.08	95.9432	25	2434.69	96.361
2s	2382.62	76.5567	27	2343.09	79.9724	28	2304.52	82.5831	29	2072.14	94.7078	30	2000.78	96.2696
31	1929.43	94.3062	32	1900.5	92.9072	33	1878.33	94.4736	34	1852.29	93.7994	35	1810.83	92.8789
36	1780.94	94.4207	37	1756.83	92.8136	38	1657.52	33.078	39	1579.41	5.18991	40	1439.6	81.6954
41	1377.89	57.5003	42	1340.28	34.9992	43	1255.43	87.5677	44	1208.18	89.992	45	1135.87	87.1397
46	1061.62	85.4256	47	912.165	89.6197	48	749.209	65.8161	49	696.177	78.9279	50	661.464	81.8898
51	612.288	89.8505	52	579.504	84.7382	53	493.688	75.7989	54	445.476	85.6119			

Compound – VIII : 4 g



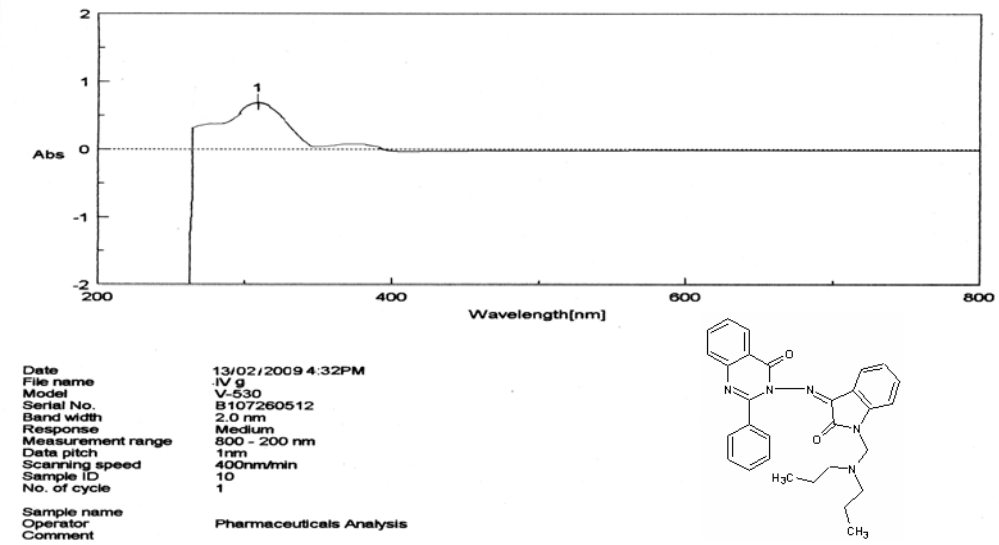
Chemical name : 1-(N,N-di-n-propylamino)-methyl-3-(2-phenyl-4-oxo-3-quinazolinylimino)-1,3-dihydro-indole-2-one

Molecular formula : $C_{29}H_{29}N_5O_2$

a) UV Spectrum

Solvent : methanol

λ_{max} : 305nm

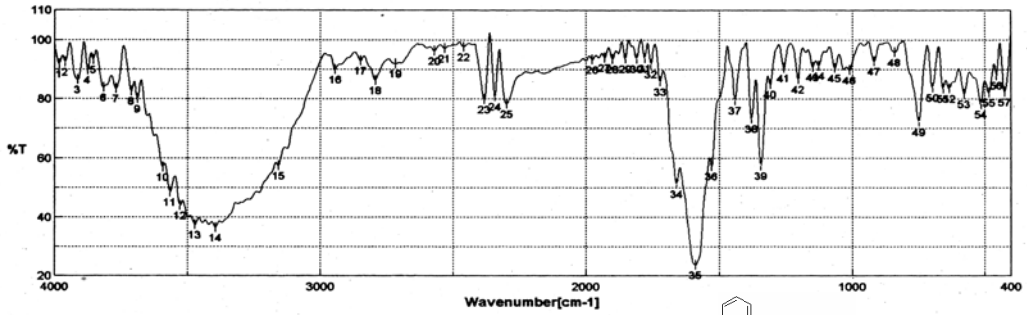


Date	13/02/2009 4:32PM
File name	IV g
Model	V-530
Serial No.	B107260512
Band width	2.0 nm
Response	Medium
Measurement range	800 - 200 nm
Data pitch	1nm
Scanning speed	400nm/min
Sample ID	10
No. of cycle	1
Sample name	
Operator	Pharmaceuticals Analysis
Comment	

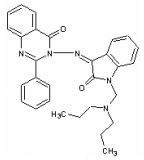
b) **Infrared spectrum**:

The IR spectrum of the above compound showed characteristic absorption bands in the following region.[TABLE NO.:11]

S.No.	Type of Vibration	Wave No (cm^{-1})
1.	Aromatic CH Stretch	3157.86
2.	Aliphatic CH Stretch	2945.73
3.	C=O of Isatin	1722.12
4.	C=N Stretch	1441.53
5.	C-N Stretch	1343.18
7.	Aromatic CH Bend	702.926

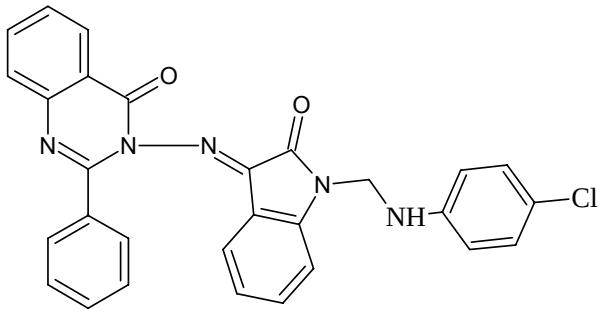


Accumulation	40	Resolution	4 cm-1
Zero Filling	ON	Apodization	Cosine
Gain	4	Scanning Speed	2 mm/sec
Date/Time	2/13/2009 0:56PM	Update	2/27/2009 6:13PM
Operator	C.Geetha		
File Name	IV g		
Sample Name	4h		
Comment			



No.	cm-1	%T	No.	cm-1	%T	No.	cm-1	%T	No.	cm-1	%T	No.	cm-1	%T
1	3983.25	91.8632	2	3959.14	92.5452	3	3913.82	86.6094	4	3875.25	89.8608	5	3854.04	93.4319
6	3817.4	83.8982	7	3770.15	83.48	8	3712.3	82.6777	9	3688.19	80.1055	10	3593.7	57.0122
11	3565.74	48.4206	12	3528.13	43.9155	13	3473.17	37.4444	14	3396.03	36.542	15	3157.86	57.4523
16	2945.73	90.0259	17	2849.31	93.0331	18	2793.38	86.4117	19	2718.17	91.96	20	2571.61	96.4022
21	2533.04	97.2098	22	2460.72	97.7702	23	2363.59	79.9146	24	2344.05	80.8396	25	2299.7	78.4035
26	1975.71	93.3613	27	1929.43	94.0502	28	1900.5	93.5806	29	1853.26	93.8747	30	1811.79	93.7556
31	1780.94	93.861	32	1756.83	91.8475	33	1722.12	85.9313	34	1660.41	51.3344	35	1590.02	23.8777
36	1529.27	57.3391	37	1441.53	79.4819	38	1379.82	73.4149	39	1343.18	57.4282	40	1308.46	85.0335
41	1257.36	90.5023	42	1203.36	86.7512	43	1147.44	90.878	44	1124.3	91.4168	45	1064.51	90.4561
46	1010.52	89.8063	47	916.986	92.9101	48	839.847	95.8933	49	747.281	72.3125	50	697.141	83.8267
51	657.607	83.5024	52	635.43	83.5913	53	578.54	81.7697	54	515.865	78.252	55	485.009	82.1779
56	455.118	88.0263	57	424.263	82.3273									

Compound – IX : 4 h



Chemical name : 1-(4-Chlorophenylamino)-methyl-3-(2-phenyl-4-oxo-3-quinazolinylimino)-1,3-dihydro-indole-2-one

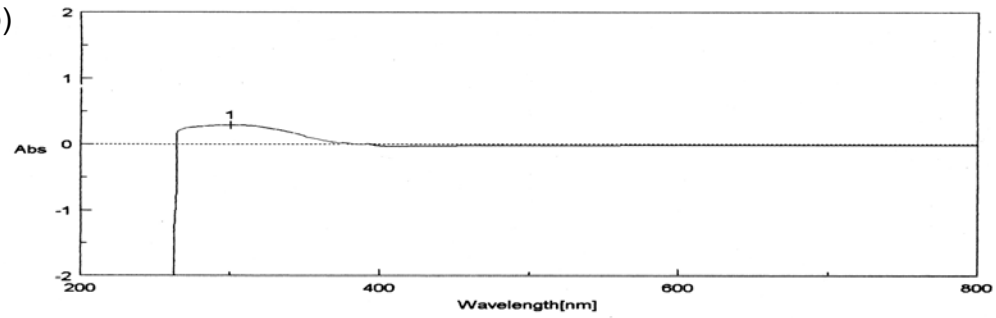
Molecular formula : $C_{29}H_{20}ClN_5O_2$

a) UV Spectrum

Solvent : methanol

λ_{max} : 305nm

b)



Date	13/02/200910:30AM
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Data pitch	1nm
Scanning speed	400nm/min
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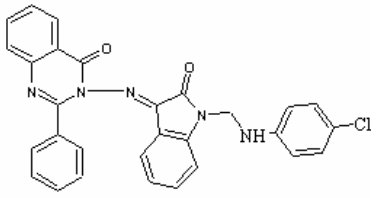
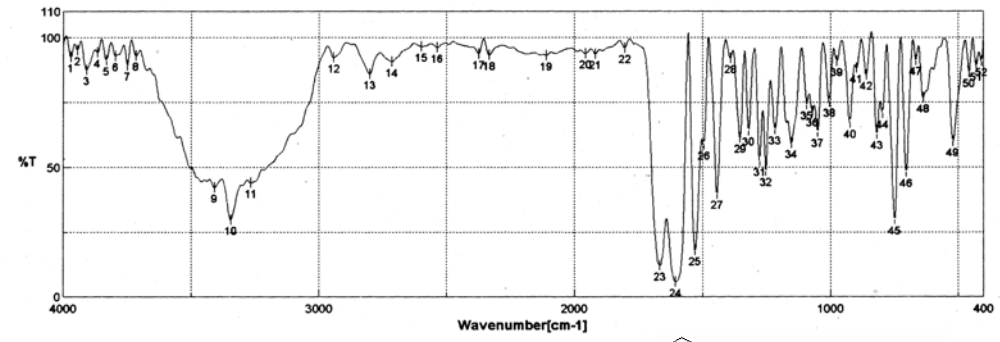
No. of cycle	1
Sample name	
Operator	Pharmaceuticals Analysis
Comment	



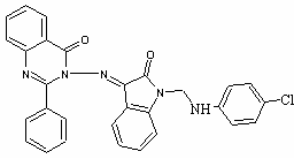
Infrared spectrum:

The IR spectrum of the above compound showed characteristic absorption bands in the following region.[TABLE NO.:12]

S.No.	Type of Vibration	Wave No (cm^{-1})
1.	NH Stretch	3264.89
2.	Aliphatic CH Stretch	2942.84
3.	C=O of Quinazolinone	1666.2
4.	C=N Stretch	1443.46
5.	C-N Stretch	1352.26
6.	Aromatic CH Bend	702.926

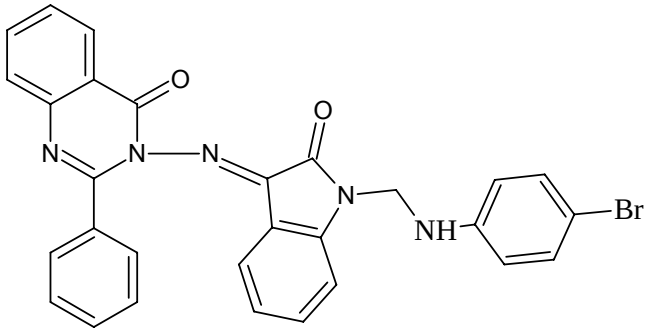


Accumulation	40	Resolution	4 cm-1
Zero Filling	ON	Apodization	Cosine
Gain	8	Scanning Speed	2 mm/sec
Date/Time	2/11/2009 3:31PM	Update	2/27/2009 6:15PM
Operator	C.Geetha		
File Name	IV h		
Sample Name	4f		
Comment			



No.	cm-1	%T	No.	cm-1	%T	No.	cm-1	%T	No.	cm-1	%T	No.	cm-1	%T
1	3970.71	92.5094	2	3945.64	95.249	3	3909.97	87.6026	4	3867.54	94.2853	5	3832.83	91.394
6	3796.19	93.0068	7	3749.9	89.351	8	3716.16	93.026	9	3409.53	42.2775	10	3345.89	29.8917
11	3264.89	44.0283	12	2942.84	92.2195	13	2802.06	85.9794	14	2715.28	90.724	15	2599.57	96.5966
16	2537.86	96.111	17	2374.91	93.8235	18	2334.41	93.2879	19	2111.67	93.2199	20	1957.39	93.9091
21	1918.82	93.7217	22	1805.05	96.0698	23	1666.2	12.2646	24	1604.48	5.98745	25	1529.27	17.9978
26	1495.53	58.8177	27	1443.46	39.8054	28	1391.39	92.0888	29	1352.82	61.3879	30	1320.04	64.1591
31	1276.65	52.5345	32	1250.61	48.6152	33	1214.93	64.7155	34	1152.26	59.2723	35	1091.51	74.3014
36	1070.3	71.5566	37	1050.05	63.6903	38	1004.73	75.1839	39	973.876	90.9333	40	922.771	67.1189
41	897.701	88.1535	42	858.168	85.5396	43	815.742	62.7734	44	794.528	70.762	45	747.281	29.8183
46	702.926	48.2323	47	665.321	91.259	48	637.358	76.7686	49	520.686	59.9677	50	457.047	86.6215
51	429.064	89.0367	52	409.799	90.9232									

Compound – X : 4 i



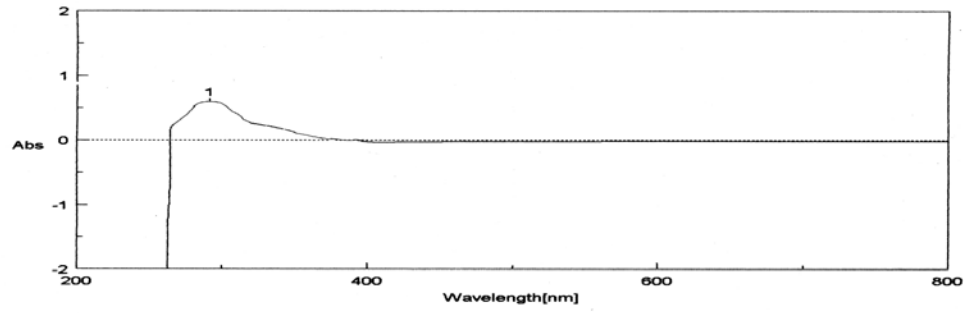
Chemical name : 1-(4-Bromophenylamino)-methyl-3-(2-phenyl-4-oxo-3-quinazolinylimino)-1,3-dihydro-indole-2-one

Molecular formula : $C_{29}H_{20}BrN_5O_2$

a) UV Spectrum

Solvent : methanol

λ_{max} : 305nm



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Band width	2.0 nm
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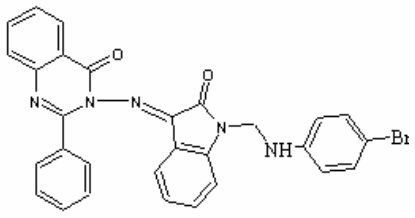
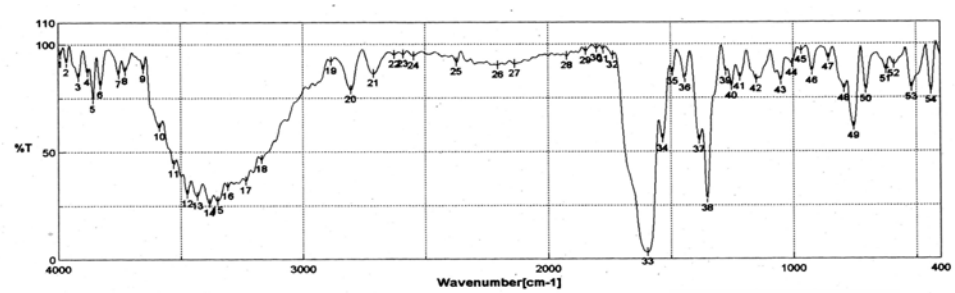
Measurement range	800 - 200 nm
Data pitch	1nm
Scanning speed	400nm/min
Sample ID	10
No. of cycle	1
Sample name	
Operator	Pharmaceuticals Analysis
Comment	



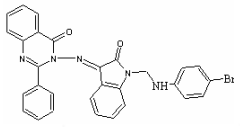
b) **Infrared spectrum**:

The IR spectrum of the above compound showed characteristic absorption bands in the following region.[TABLE NO.:13]

S.No.	Type of Vibration	Wave No (cm^{-1})
1.	NH Stretch	3234.13
2.	Aromatic CH Stretch	3171.36
3.	Aliphatic CH Stretch	2885.95
4.	C=O of Isatin	1736.58
5.	C=N Stretch	1442.49
6.	C-N Stretch	1350.89
7.	Aromatic CH Bend	701.962

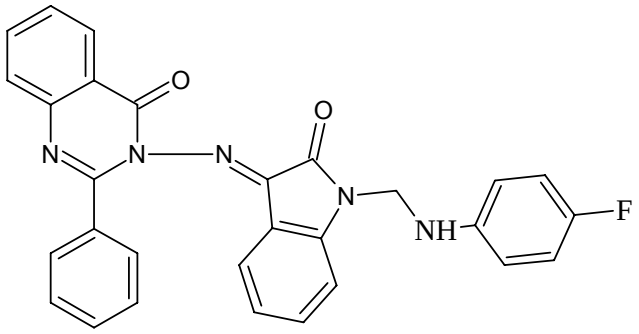


Accumulation	40	Resolution	4 cm-1
Zero Filling	ON	Apodization	Cosine
Gain	8	Scanning Speed	2 mm/sec
Date/Time	2/11/2009 3:27PM	Update	2/27/2009 6:18PM
Operator	C.Geetha		
File Name	IV i		
Sample Name	4i		
Comment			



No.	cm-1	%T	No.	cm-1	%T	No.	cm-1	%T	No.	cm-1	%T	No.	cm-1	%T
1	3991.93	95.324	2	3966.86	91.5843	3	3918.64	84.7506	4	3861.04	67.0786	5	3857.9	74.4808
6	3827.04	81.0672	7	3752.8	85.9678	8	3726.76	87.4383	9	3652.52	88.4379	10	3586.95	61.52
11	3528.13	44.3455	12	3474.13	30.5029	13	3432.67	29.423	14	3382.53	26.1338	15	3350.71	27.3502
16	3308.29	33.8636	17	3234.04	36.5021	18	3171.36	48.5489	19	2885.95	92.0489	20	2805.92	78.8465
21	2713.35	88.3168	22	2627.54	95.2156	23	2590.9	95.3051	24	2547.5	94.6428	25	2373.94	91.7512
26	2205.2	90.2531	27	2136.74	90.8583	28	1923.65	94.4859	29	1846.51	96.7457	30	1802.15	98.0032
31	1774.19	97.3852	32	1736.58	94.6807	33	1595.81	3.20649	34	1534.1	58.0142	35	1492.63	86.9709
36	1442.49	83.903	37	1383.68	55.3426	38	1350.89	28.1101	39	1274.72	87.3088	40	1251.58	80.2504
41	1217.83	84.5297	42	1151.29	83.5883	43	1051.01	82.7826	44	1004.73	90.9628	45	967.126	96.9766
46	921.807	87.3201	47	855.275	93.4462	48	793.564	79.1603	49	754.031	61.5811	50	701.962	78.6105
51	621.931	87.9294	52	587.218	90.3676	53	517.793	79.5577	54	437.762	77.9906			

Compound – XI : 4 j



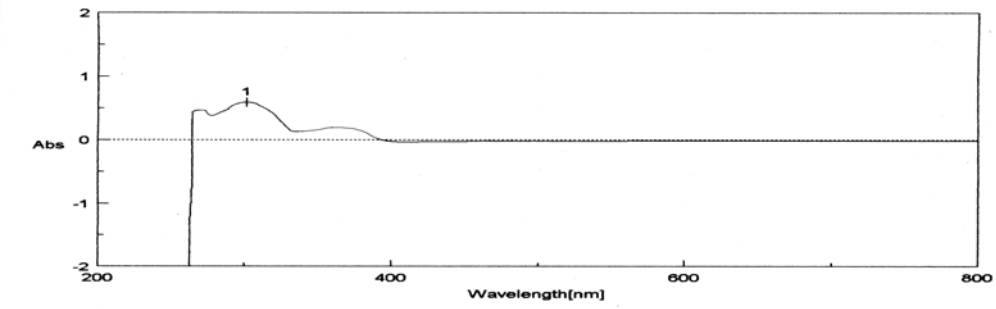
Chemical name : 1-(4-Flurophenylamino)-methyl-3-(2-phenyl-4-oxo-3-quinazolinylimino)-1,3-dihydro-indole-2-one

Molecular formula : $C_{29}H_{20}FN_5O_2$

a) UV Spectrum

Solvent : Methanol

λ_{max} : 305nm



Date	13/02/2009 4:52PM
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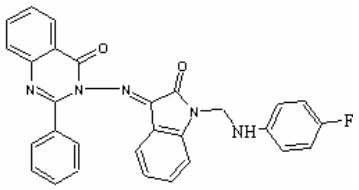
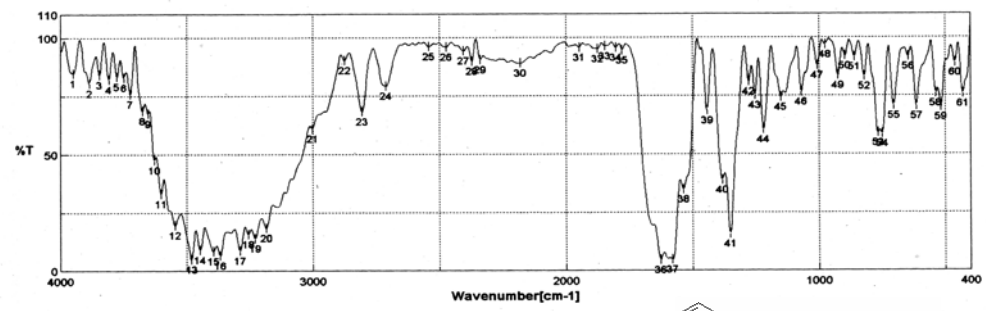
Data pitch	1nm
Scanning speed	400nm/min
Sample ID	10
No. of cycle	1
Sample name	
Operator	Pharmaceuticals Analysis
Comment	



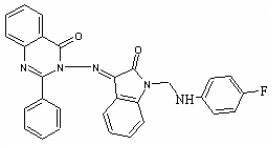
b) **Infrared spectrum**:

The IR spectrum of the above compound showed characteristic absorption bands in the following region.[TABLE NO.:14]

S.No.	Type of Vibration	Wave No (cm^{-1})
1.	NH Stretch	3230.18
2.	Aromatic CH Stretch	3186.79
3.	C=O of Isatin	1777.08
4.	C=N Stretch	1442.49
5.	C-N Stretch	1349.93
6.	Aromatic CH Bend	703.89



Accumulation	40	Resolution	4 cm-1
Zero Filling	ON	Apodization	Cosine
Gain	16	Scanning Speed	2 mm/sec
Date/Time	2/11/2009 3:29PM	Update	2/27/2009 6:21PM
Operator	C.Geetha		
File Name	IV j		
Sample Name	4d		
Comment			



No.	cm-1	%T	No.	cm-1	%T	No.	cm-1	%T	No.	cm-1	%T	No.	cm-1	%T
1	3849.5	84.7999	2	3805.86	80.5354	3	3844.4	84.1194	4	3808.72	82.2202	5	3775.84	83.3643
6	3748.94	82.9545	7	3722.91	75.8636	8	3675.66	68.6733	9	3653.48	67.5897	10	3628.41	47.6101
11	3602.38	33.0555	12	3546.45	19.7084	13	3490.88	4.99798	14	3447.13	9.12998	15	3395.07	8.47423
16	3367.1	6.76018	17	3289.98	8.83084	18	3257.18	15.9113	19	3230.18	14.1036	20	3186.79	18.4731
21	3003.59	61.0799	22	2876.31	90.2636	23	2807.85	88.3197	24	2712.39	79.2559	25	2541.72	96.1349
26	2474.22	96.0404	27	2404.8	94.2752	28	2372.01	89.8572	29	2338.27	90.543	30	2180.13	89.0375
31	1948.72	95.8325	32	1875.43	95.1553	33	1846.51	96.2796	34	1802.15	95.754	35	1777.08	94.6038
36	1626.66	4.76494	37	1580.38	4.93627	38	1536.99	35.0575	39	1442.49	68.7078	40	1382.71	39.1361
41	1349.93	15.9316	42	1277.61	81.0522	43	1253.5	75.2849	44	1219.76	80.6313	45	1151.29	74.505
46	1089.33	76.5735	47	1006.66	88.0607	48	975.804	97.0292	49	923.736	83.7019	50	896.737	92.0701
51	860.096	91.7917	52	820.563	83.3372	53	784.837	59.0931	54	749.209	58.8534	55	703.89	70.8224
56	646.036	91.878	57	613.252	70.6048	58	536.114	76.0028	59	516.829	70.146	60	461.868	89.271

ANTIMICROBIAL SCREENING

APPARATUS AND CHEMICALS REQUIRED

Sterile discs	:	Hi Media
Standard discs of drugs	:	Hi Media
Sterile swab	:	Hi Media
Non- absorbent cotton	:	Rama Raju Surgical cotton Ltd.
Conical flask (250 ml)	:	Borosil
Test Tubes	:	Borosil
Petri dishes	:	SD Fine - Chem Ltd.
Micropipettes	:	VARI pipettes (Hi- Tab Lab)
Hot air oven	:	Technico Equipments
Autoclave	:	Universal Autoclave
Laminar Flow Unit	:	CLEAN AIR Instruments Inc.
Incubator	:	Technico Incubator
Micro tips	:	Tarsons

The antibacterial and antifungal screening were carried out in the Pharmaceutical Biotechnology Laboratory, College of Pharmacy, SRIPMS, Coimbatore.

SCREENING FOR ANTIBACTERIAL ACTIVITY[64,65]

Media: Mueller- Hinton agar

Mueller Hinton broth gelled by the addition of 2% agar of bacteriological grade.

Ingredients

Casein enzymic hydrolysate	:	17.5 gL^{-1}
Beef infusion	:	300 gL^{-1}
Soluble starch	:	1.5 gL^{-1}
Final pH at 25^0C	:	7.4 ± 0.2

Preparation

The ingredients were dissolved in distilled water with the aid of heat and pH was adjusted to 7.2 - 7.6 using dilute alkali or acid.

Sterilization

15-30 ml of Mueller Hinton agar was transferred to petriplate and sealed. It was then autoclaved at a pressure of 15 psi (121^oC) for not less than 15 minutes.

Organisms used

Staphylococcus aureus NCIM 5021, *Bacillus subtilis* NCIM 2010, *Pseudomonas aeruginosa* NCIM 5029 and *Escherichia coli* NCIM 2911 were procured from National Chemical Laboratory, Pune and stored in the Pharmaceutical Biotechnology Laboratory, College of Pharmacy, SRIPMS, Coimbatore-44. The strains were confirmed for their purity and identity by

Gram's staining method and their characteristic biochemical reactions. The selected strains were preserved by subculturing them periodically on nutrient agar slants and storing them under frozen conditions. For the study, fresh 24 h broth cultures were used after standardization of the culture.

Working conditions

The entire work was done using vertical laminar flow hood so as to provide aseptic conditions. Before commencement of the work, air sampling was carried out using a sterile nutrient agar plate and exposing it to the environment inside the hood. After incubation it was checked for the growth of microorganism and absence of growth confirmed aseptic working conditions.

Preparation of inoculum

The inoculum for the experiment was prepared fresh in Mueller Hinton broth from preserved frozen slants. It was incubated at 37^{o}C for 18-24 hrs and used after standardization.

Drugs used	:	quinazolinyl mannich base
Standard used	:	Ciprofloxacin (5mcg/disc)
Vehicle used	:	Dimethyl sulphoxide

ANTIBACTERIAL SCREENING

Mueller Hinton agar plates were prepared aseptically to get a thickness of 5-6 mm. The plates were allowed to solidify and inverted to

prevent the condensate falling on the agar surface. The plates were dried at 37^{o}C before inoculation.

The organisms *Staphylococcus aureus* NCIM 5021, *Bacillus subtilis* NCIM 2010, *Pseudomonas aeruginosa* NCIM 5029 and *Escherichia coli* NCIM 2911 were inoculated in the plates prepared earlier, by dipping a sterile swab in the previously standardized inoculum, removing the excess of inoculum by pressing and rotating the swab firmly against the sides of the culture tube above the level of the liquid and finally streaking the swab all over the surface of the medium 3 times, rotating the plates through an angle of 60^{o} after each application. Finally the swab was pressed round the edge of the agar surface. It was allowed to dry at room temperature, with the lid closed. The sterile disc containing test drugs, standard and blank were placed on the previously inoculated surface of the Mueller Hinton agar plate and it was kept in the refrigerator for one hour to facilitate uniform diffusion of the drug.

Petriplates were prepared and they were then incubated for 18-24 h. Observations were made for zone of inhibition around the discs and compared with that of standard. All the compounds synthesized were tested for antibacterial activity against gram-positive and gram-negative bacteria. Saturated solutions (100µg/disc) of the compounds were studied for activity.

ANTIBACTERIAL SCREENING

Microorganism used as Gram +ve bacteria : *Staphylococcus aureus, Bacillus subtilis*

Microorganism used as Gram -ve bacteria : *Escherichia coli, Pseudomonas aeruginosa*

Vehicle used : Dimethylsulphoxide [TABLE NO.:15]

S.No	Compound Code	Diameter of Zone of Inhibition (in mm)			
		Bacillus subtilis **NCIM 2010**	***Staphylococcus aureus*** **NCIM 5021**	***Escherichia coli*** **NCIM 2911**	***Pseudomonas aeruginosa*** **NCIM 5029**
		100µg/disc	**100µg/disc**	**100µg/disc**	**100µg/disc**
1	4 a	-	-	-	-
2	4 b	-	10	-	-
3	4 c	-	-	-	-
4	4 d	10	-	-	-
5	4 e	-	-	-	-
6	4 f	<10	-	-	-
7	4 g	10	-	-	-
8	4 h	-	-	-	-
9	4 i	-	-	-	-
10	4 j	-	-	-	-
11	4 k	-	-	-	-
12	Standard (Ciprofloxacin) 5 mcg/disc	31	30	29	32

Figure A showing the antibacterial activity of quinazolinyl mannich base against *Bacillus Subtilis* at 100µg/disc (saturated solution)

Figure B showing the antibacterial activity of quinazolinyl mannich base against *Staphylococcus aureus* at 100µg/disc(saturated solution)

SCREENING FOR ANTIFUNGAL ACTIVITY

Media : Sabouraud Dextrose Agar

Ingredients

Mycological peptone	:	10 g
Dextrose	:	40 g
Agar	:	15 g
Final pH at 25^0C	:	5.4 $\pm$ 0.2

Water to make 1000 ml

Preparation

65 g of Sabouraud dextrose agar was suspended in 1000 ml of distilled water and boiled to dissolve the medium completely.

Sterilization

15-30 ml of Sabouraud dextrose agar was transferred to petriplate and sealed. It was then autoclaved at a pressure of 15 psi (121^oC) for not less than15 minutes.

Organism used

Candida albicans NCIM 3100 and *Aspergillus niger* NCIM 545 were procured from National Chemical Laboratory, Pune and stored in the Pharmaceutical Biotechnology Laboratory, College of Pharmacy, SRIPMS, Coimbatore.

Drugs used	:	Quinazolinyl mannich base
Standard used	:	Fluconazole (25mcg/disc)
Vehicle used	:	Dimethyl sulphoxide

ANTIFUNGAL SCREENING

Sabouraud dextrose agar plates were prepared aseptically to get a thickness of 5-6 mm. The plates were allowed to solidify and inverted to prevent the condensate falling on the agar surface. The plates were dried at 25^{o}C just before inoculation.

The organisms (*Candida albicans* NCIM 3100 and *Aspergillus niger* NCIM 545*)* were inoculated in the plates prepared earlier by dipping sterile swab in the inoculum, removing the excess of inoculum by pressing and rotating the swab firmly against the sides of the culture tube above the level of the liquid and finally streaking a swab all over the surface of the medium three times, rotating the plates through the angle of 60^{o} after each application. Finally the swab was pressed round the edges of the agar surface. It was left to dry at room temperature with the lid closed. Sterile discs containing the test, standard and blank were placed in the petridish aseptically. Saturated solutions of the test samples were used.

Petriplates were prepared and they were incubated at 25^{o}C for 24-48 h, after placing them in the refrigerator for one hour to facilitate uniform diffusion. Observations were made for the zone of inhibition around the discs and compared with that of Fluconazole, the standard. All the compounds were tested for antifungal activity.

RESULT AND DISCUSSION OF ANTIMICROBIAL STUDIES

Anti-bacterial studies

All the newly synthesized compounds were screened for anti-bacterial activity.

Gram- positive organism used:

- *Staphylococcus aureus* NCIM 5021,
- *Bacillus Subtilis* NCIM 2010.

Gram-negative organism used:

- *Escherichia coli* NCIM 2911,
- *Pseudomonas aeruginosa* NCIM 3100.

Concentrations of 100 µg/disc (saturated solution) were used for all the test compounds and the results were compared with the standard drug Ciprofloxacin at 5µg/disc, against Gram positive and Gram negative bacteria using dimethyl sulphoxide (DMSO) as vehicle.

Among the synthesized compounds, **4d** (N- methyl piperazinyl derivative), **4g** (N, N- dipropyl amino derivative) at 1000µg/disc concentration was found to show mild activity against *B.subtilis*.

The compound **4b** (morpholinyl derivative) at 100 µg/disc concentration was found to show mild activity against *S. aureus.*

None of the compounds showed activity against *P. aeruginosa* and *E. coli*. Anti-bacterial activities exhibited by the synthesised compounds were not comparable to the standard drug Ciprofloxacin.

Antifungal studies

All newly synthesized mannich bases of isatin were screened for antifungal activity against *Candida albicans* NCIM 3100 and *Aspergillus niger* NCIM 545 using Fluconazole (25 µg/disc) as standard and Dimethylsulphoxide (DMSO) as the vehicle. Concentrations of 100 µg/disc (saturated solution) of synthesized compounds were used for evaluating all the test compounds. All the compounds were found to be inactive against both the organisms.

ANTIOXIDANT STUDIES

FREE RADICAL SCAVENGING ACTIVITY BY DPPH ASSAY METHOD

Chemicals used

- 2,2-Diphenyl-1-Picrylhydrazyl(DPPH)
- Methanol
- Ascorbic acid

Preparation of solutions

Free radical scavenging activity of the test compounds were determined by DPPH assay method and compared with ascorbic acid as standard.

- **Preparation of 0.2 mM drug solution**

  Weight equivalent to 0.2 mM was taken in 10 ml standard flasks made up to the mark with methanol and suitably diluted to get 0.2 mM concentration.

- **Preparation of 0.2 mM DPPH solution**

  0.008 g of DPPH was taken in a 100 ml standard flask, dissolved in methanol. 1ml of the above solution was taken and diluted in 10ml standard flask with methanol to get a concentration of 0.2mM.

- **Preparation of 0.2 mM standard solution**

  0.035g of ascorbic acid was taken in 100 ml standard flask, dissolved in methanol and the volume was adjusted to 100ml with methanol. 1ml of the above solution was taken in a 10ml standard flask and the volume was made up with methanol.

- **Procedure for evaluation of antioxidant activity**

1.5 ml of 0.2 mM of DPPH solution was added to 1.5 ml of 0.2mM concentration of the drug solutions. Another series of solutions were prepared by taking 1.5 ml of different concentrations of drug solutions and 1.5 ml of methanol. The above solutions were allowed to react at room temperature for 30 min. After 30 minutes the absorbance values were measured at 517 nm and percentage of scavenging activity was calculated using the following formula :

Scavenging activity (%) = [(Ab + As) – Am / Ab] X 100

Ab = Absorbance of 1.5 ml DPPH solution + 1.5 ml methanol

Am= Absorbance of 1.5 ml DPPH solution + 1.5 ml drug solution

As= Absorbance of 1.5 ml drug solution + 1.5 ml methanol

Experiments were carried out in triplicate.

DPPH Free Radical Scavenging Activity of Test Compounds [TABLE NO.:16]

S.	Compound	Trial	Absorbance	Free radical scavenging activity (%)

No.	Code	No.	Am	As	Ab	Scavenging activity (%)	[a]Scavenging activity(%)
1.	4 a	1	0.614	0.171		64	61±6.42
		2	0.527	0.088		66	
		3	0.628	0.084		54	
2.	4 b	1	0.687	0.106		53	53±0.58
		2	0.702	0.109		54	
		3	0.695	0.110		53	
3.	4 c	1	0.473	0.088		69	73±3.21
		2	0.493	0.172		75	
		3	0.489	0.168		74	
4.	4 d	1	0.786	0.314		62	64±2.08
		2	0.814	0.308	1.240	61	
		3	0.820	0.308		58	
5.	4 e	1	0.735	0.344	1.290	68	70±2.89
		2	0.688	0.342		73	
		3	0.740	0.348	1.235	68	
6.	4 f	1	0.893	0.267		50	51±1.16
		2	0.880	0.264		52	
		3	0.887	0.269		50	
7.	4 g	1	1.531	0.697		33	33±1.53
		2	1.527	0.684		35	
		3	1.526	0.685		32	
8.	4 h	1	1.145	0.063		13	13±2.52
		2	1.146	0.062		16	

		3	1.146	0.068		11	
9.	4 i	1	0.987	0.112		29	31±2.08
		2	0.985	0.123		33	
		3	0.980	0.124		30	
10.	4 j	1	0.884	0.211		45	46±1.53
		2	0.888	0.214		48	
		3	0.887	0.219		46	

Free radical scavenging activity of the standard, Ascorbic acid= 97±0.35%

[a] Results are mean ± standard deviation (S. D)

RESULTS AND DISCUSSION

From the results of antioxidant activity screening of the newly synthesized compounds, it was found that **4c** (N-methyl aniline derivative) exhibited the maximum free radical scavenging activity of 73% at the final concentration of 0.2mM.

Among the tested compounds **4a** (piperidinyl derivative), **4b** (morpholinyl derivative), **4d** (N-methly piperazinyl derivative), **4e** (N, N-dimethyl amino derivative), **4f** (N, N-diethyl amino derivative), **4j** (4-fluorophenyl amino derivative) showed free radical scavenging activity in the range 40-70%, while the rest of the compounds showed less than 40% free radical scavenging activity.

Ascorbic acid which was used as the standard in this screening showed free radical scavenging activity of 97% at 0.1mM concentration.

None of the compounds exhibited superior activity compared to the standard ascorbic acid.

SUMMARY AND CONCLUSION

SUMMARY

Synthesis of 1-substituted-methyl-3-(2-phenyl-4-oxo-3-quinazolinylimino)-1, 3-dihydro-indole-2-one 4(a-k)

In this scheme eleven different isatin based mannich bases of quinazolin-4-one were synthesized by four step process.

- First step was the synthesis of 2- phenyl benzoxazin-4-one.
- In the second step the benzoxazin-4-one was converted to 3-amino-2-phenylquinazol-4-one by treating with hydrazine hydrate using ethanol as the solvent.
- In the third step, Schiff's base was synthesized by the condensation of the keto group of isatin with 3-amino-2-phenylquinazol-4-one.
- In the fourth step, N- Mannich bases of the above Sciff's base were synthesized by the reaction of amino group of isatin with formaldehyde and various primary and secondary amines.

Yield of most of the derivatives by the conventional method (reaction time: 1 hour) ranged from 60-72% and in the microwave method (reaction time: 3 min) ranged between 75-89%. Structures of the compounds were confirmed by UV, IR, PMR and Mass spectral datas.

BIOLOGICAL ACTIVITY SCREENING

Mannich bases of isatin are known to possess wide variety of biological activity. Hence the newly synthesized compounds were screened for antimicrobial and antioxidant activity.

ANTIBACTERIAL STUDIES

- Saturated concentration(100µg/disc) of all the test compounds were used and the results were compared with that of the standard Ciprofloxacin at 5 mcg/disc concentration, against Gram positive and Gram negative bacteria using dimethyl sulphoxide (DMSO) as the vehicle.
- Among the synthesized compounds, **4d** (N-methyl piperazinyl derivative), **4g** (N, N- dipropyl amino derivative) at 100µg/disc concentration was found to show mild activity against *B.subtilis*.
- The compound **4b** (morpholinyl derivative) at 100 µg/disc concentration was found to show mild activity against *S. aureus.*

ANTIFUNGAL STUDIES

All newly synthesized mannich bases were screened for antifungal activity against *Candida albicans* NCIM 3100 and *Aspergillus niger* NCIM 545 using Fluconazole (25 µg/disc) as standard and Dimethylsulphoxide (DMSO) as the vehicle. Concentrations of 100 µg/disc (saturated solution) of synthesized compounds were used for evaluating all the test compounds. All the compounds were found to be inactive against both the organisms.

ANTI-OXIDANT STUDIES

- Free radical scavenging activity was done by DPPH assay method using ascorbic acid as the standard.

- Among the newly synthesized compounds, Compound **4c** (N- methyl aniline derivative) exhibited the maximum free radical scavenging activity at the final concentration of 0.2mM.
- Among the tested compounds **4a** (piperidinyl derivative), **4b** (morpholinyl derivative), **4d** (N- methyl piperazinyl derivative), **4e** (N, N-dimethyl amino derivative), **4f** (N, N-diethyl amino derivative), **4j** (4-flurophenyl amino derivative) showed free radical scavenging activity in the range 40-70%, while the rest showed less than 40%.
- Ascorbic acid which was used as the standard in this screening showed free radical scavenging activity of 97% at 0.1mM concentration. None of the compounds exhibited superior activity compared to the standard ascorbic acid.

CONCLUSION

Based on the observations made from the results of synthetic work, characterization data, antimicrobial screening and screening of free radical scavenging activity, the following conclusions were drawn.

- Microwave method of synthesis proved to be more efficient than the conventional method with respect to less reaction time and increased percentage yield of the product. This was especially observed for the N, N-dipropyl amino derivative **4g** where the % yield of the product increased by 17% in microwave method of synthesis.
- From the results obtained in the antibacterial screening, it was seen that, the presence of N-methyl piperazinyl substituent (**4d**) and N, N-dipropylamino substituent (**4g**) in the mannich bases of quinazolione

imparted mild antibacterial activity against *B. subtilis* and the presence of morpholinyl substituent (**4b**) exerted mild activity against *S. aureus.*

- Mannich bases of qunazolinyl having N-methylphenylamino substituent (**4c**) and N, N-dimethylamino substituent (**4e**) showed the highest free radical scavenging capacity for DPPH than the rest of the compounds synthesized.
- Among the synthesized compounds **4d, 4g** and **4b** can be taken up as lead moieties for further structural modification to enhance the antibacterial activity.
- Structural variation can be attempted on compound **4c** and **4e** for improving the antioxidant potential of the respective Mannich bases.

SUMMARY AND CONCLUSION

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Based on the observations made from the results of synthetic work, characterization data, antimicrobial screening and screening of free radical scavenging activity, the following conclusions were drawn.

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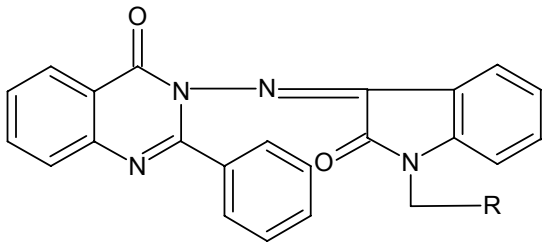
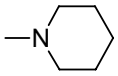
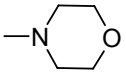
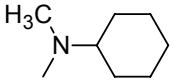
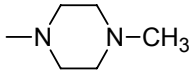
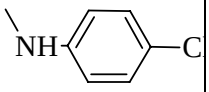
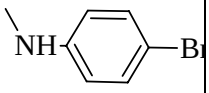
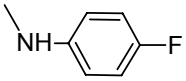
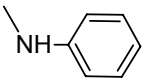
LIST OF NEWLY SYNTHESIZED COMPOUNDS

SCHEME - I



1-substituted methyl-3-(2-phenyl-4-oxo-3-quinazolinylimino)-1, 3- dihydro-indol-2-one 4 (a-k)

COMPOUND CODE	R	CHEMICAL NAME
IV a		1-Piperidino-methyl-3-(2-phenyl-4-oxo-3-quinazolinylimino)-1,3-dihydro-indole-2-one
IV b		1-Morpholino-methyl-3-(2-phenyl-4-oxo-3-quinazolinylimino)-1,3-dihydro-indole-2-one
IV c		1-(N-methy phenylamino)-methyl-3-(2-phenyl-4-oxo-3-quinazolinylimino)-1,3-dihydro-indole-2-one
IV d		1-(N-methy piperazino)-methyl-3-(2-phenyl-4-oxo-3-quinazolinylimino)-1,3-dihydro-indole-2-one
IV e	$-N(CH_3)_2$	1-(N,N-dimethylamino)-methyl-3-(2-phenyl-4-oxo-3-quinazolinylimino)-1,3-dihydro-indole-2-one
IV f	$-N(C_2H_5)_2$	1-(N,N-diethylamino)-methyl-3-(2-phenyl-4-oxo-3-quinazolinylimino)-1,3-dihydro-

		indole-2-one
IV g	$-N(C_3H_7)_2$	1-(N,N-di-n-propylamino)-methyl-3-(2-phenyl-4-oxo-3-quinazolinylimino)-1,3-dihydro-indole-2-one
IV h		1-(4-Chlorophenylamino)-methyl-3-(2-phenyl-4-oxo-3-quinazolinylimino)-1,3-dihydro-indole-2-one
IV i		1-(4-Bromophenylamino)-methyl-3-(2-phenyl-4-oxo-3-quinazolinylimino)-1,3-dihydro-indole-2-one
IV j		1-(4-Fluorophenylamino)-methyl-3-(2-phenyl-4-oxo-3-quinazolinylimino)-1,3-dihydro-indole-2-one
IV k		1-Phenylamino-methyl-3-(2-phenyl-4-oxo-3-quinazolinylimino)-1,3-dihydro-indole-2-one

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